

Sodium Oxybate Oral Solution

NDA 22-531

Joint Meeting of the Arthritis Drugs Advisory Committee
And the Drug Safety and Risk Management Advisory Committee

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Jazz Pharmaceuticals, Inc.
3180 Porter Drive
Palo Alto, CA 94304

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACR	American College of Rheumatology
AE	Adverse event
AHI	Apnea Hypopnea Index
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
BDI-II	Beck Depression Inventory-II
BMI	Body mass index
BOCF	Baseline observation carried forward
CAP	Cyclic alternating pattern
CDC	Centers for Disease Control and Prevention
CGI-c	Clinical Global Impression of Change
CGI-s	Clinical Global Impression of Severity
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C _{max}	Maximum plasma drug concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPF	Central Processing Function
CRF	Case report form
CSR	Clinical study report
DAARP	Division of Anesthesia, Analgesia, and Rheumatology Products
DAWN	Drug Abuse Warning Network
DCC	Data Coordination Center
DIS	Diagnostic Interview Schedule
DLX	Duloxetine
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV—Text Revision
DSST	Digit Symbol Substitution Test

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

EC	Ethics committee
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
FM	Fibromyalgia
FOSQ	Functional Outcomes of Sleep Questionnaire
g	Grams
GABA	Gamma-aminobutyric acid
GABA _B	Gamma-aminobutyric acid B-subtype
GAD	Generalized Anxiety Disorder
GBL	Gamma-butyrolactone
GHB	Gamma-hydroxybutyrate
GHBR	Gamma-hydroxybutyrate receptor
HRQoL	Health-related quality of life
IMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IV	Intravenous
JS	Jenkins Sleep Scale
LOCF	Last observation carried forward
LRZ	Lorazepam
LS	Least squares
M1-TRM	Tramadol metabolite (O-desmethyltramadol)
mcg	Micrograms
MCID	Minimal clinically important difference

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

MDE	Major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini International Neuropsychiatric Interview
mm	Millimeter
MMRM	Mixed model repeated measures
MTPS	Manual tender point survey
N	Number (of subjects)
N/A or NA	Not applicable
NADP ⁺	Nicotinamide adenine dinucleotide phosphate
NDA	New drug application
NFLIS	National Forensic Laboratory Information System
NREM	Non-rapid eye movement
NSAIDs	Non-steroidal anti-inflammatory drugs
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials (now Outcome Measures in Rheumatology)
OR	Odds ratio
OSAS	obstructive sleep apnea syndrome
OTC	Over-the-counter
PCS	Physical Component Summary
PD	Pharmacodynamic
PGI-c	Patient Global Impression of Change
PI	Prescribing information (product label)
PK	Pharmacokinetics
PSG	Polysomnography
RCT	Randomized controlled trial
REM	Rapid eye movement
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SAMHSA	Substance Abuse & Mental Health Services Administration

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF-36	Short Form-36 Questionnaire, version 2
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SXB	Sodium oxybate
$t_{1/2}$	Elimination half-life
T_{\max}	Time to maximum plasma concentration
TRM	Tramadol
VAS	Visual analog scale

EXECUTIVE SUMMARY

Fibromyalgia is a chronic pain condition affecting 3 to 6 million people in the United States. In addition to unremitting and often severe physical pain, patients suffer fatigue and disturbed sleep that lowers their pain threshold, an impaired ability to function in everyday life, financial hardship from lowered productivity and medical costs, and emotional and mental duress, often exacerbated by years of misdiagnosis and skepticism. Sodium oxybate offers an important new therapeutic option for these patients, providing substantial benefits across multiple symptom domains. This application seeks approval for the 4.5 and 6 g/night doses of sodium oxybate, with a proposed indication for the treatment of fibromyalgia.

Sodium oxybate, the sodium salt of gamma-hydroxybutyrate (GHB; an endogenous neurotransmitter), is a Schedule III substance that has been commercially available in the US as Xyrem[®] (sodium oxybate) oral solution since 2002. It is approved in the US for the treatment of excessive daytime sleepiness and cataplexy in narcolepsy, and is available in Europe and Canada for the treatment of various symptoms associated with narcolepsy. The effective dose range in narcolepsy is 6 to 9 g per night, with a recommended starting dose of 4.5 g per night. Doses are administered as two equally divided doses taken at bedtime and 2.5 to 4 hours later. Sodium oxybate is considered by the American Academy of Sleep Medicine to be a standard of care for the treatment of cataplexy, excessive daytime sleepiness, and disrupted sleep due to narcolepsy. Approximately 35,000 patients in the US have used sodium oxybate in the nearly 8 years since its first approval, with a total estimated postmarketing exposure of 31,645 patient-years.

The current risk evaluation and mitigation strategy (REMS) program for the marketed product, Xyrem, has been functioning for nearly 8 years to mitigate both risks to the individual patient and societal risks. Individual patient risks are mitigated through prescriber and patient education, documentation of safe use conditions for patients, and clear warnings about sodium oxybate's central nervous system- (CNS-) and respiratory-depressant effects and the potential for suicidality and depression in the physician labeling and the patient Medication Guide. The REMS is an active system with multiple direct conversations with patients that provide them opportunities to ask questions and seek advice about the information they are given. Societal risks of abuse, misuse, and diversion are addressed through a well-controlled, interactive distribution system, physician and patient enrollment in the REMS program, monitoring of early refill requests and other instances of potential abuse, strong warnings about the risks of abuse and misuse, which augment the restrictions that derive from sodium oxybate's status as a Schedule III controlled substance. Although no REMS program can prevent all risk, the Xyrem REMS has been effective in mitigating the risks associated with this product. The proposed REMS for the new fibromyalgia indication for sodium oxybate has the same proven design as the existing program (see [Section 5](#)).

Fibromyalgia: Clinical Characterization and Impact

Fibromyalgia is a chronic disease characterized by widespread pain for at least 3 months and pain in at least 11 of 18 anatomically defined tender points ([Wolfe et al. 1990](#)). Significant pain levels in fibromyalgia have been shown to persist over long periods ([Wolfe et al. 1997a](#)). In addition to pain and tenderness, patients suffer a constellation of often debilitating symptoms, including fatigue, decreased ability to function in daily life, poor sleep, decreased health-related quality of life, stiffness, depression, and anxiety.

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The condition affects all aspects of a patient's life: families are affected, personal relationships suffer, work becomes difficult or impossible, and simple errands involve balancing pain and fatigue against need. Patients with fibromyalgia describe the effects of this often debilitating condition.

It's heartbreaking to have this disease. The people in my life don't understand or get angry with me for my seemingly lack of interest in doing things, it's not that I don't want to spend time with them, it's the disease. I'm constantly fatigued and weak. I miss out on many things I enjoy doing, because of this disease & the chronic pain....Just because I can do a thing one day, that doesn't mean I will be able to do the same thing the next day or next week. I may be able to take that walk after dinner; the next day or even in the next hour I may not be able to walk to the fridge to get a glass of water because of the intense pain throughout my body has taken it's toll. My muscles have begun to cramp and lock up; I feel weak & tired. And there are those who say "but you did that yesterday!" "What is your problem today?" The hurt I experience at those words scars me so deeply that I have let my family down again; and still they don't understand....

--40-45 year old woman ([The Experience Project 2010](#))

I'm a man...able to do anything. The head of my family...People used to respect me, and now how can anyone respect what I've become? Weak, frail, in pain night and day, tired all the time, and not enough energy to do anything.

--Anonymous fibromyalgia patient ([Yunus 2009](#))

The impact of fibromyalgia on a patient's life is best assessed scientifically by the use of the Fibromyalgia Impact Questionnaire (FIQ), a widely used, validated instrument that covers multiple aspects of impact: physical impairment, not feeling good, work missed, difficulty with work, pain, fatigue, tiredness upon awakening, stiffness, anxiety, and depression ([Burckhardt et al. 1991](#)). The FIQ score is a strong predictor of economic and clinical outcomes, such as disability and improvement ([Bennett et al. 2009](#)). Patients with moderate to high FIQ scores (50 to 74 on a 0-100 scale) have been shown to have work disability rates as high as 35%, and those with scores above 75 have work disability rates as high as 83%, with odds ratios for work disability of 5.43 (95% confidence interval [CI] 1.75-16.79) and 35.00 (95% CI 8.70-140.87), respectively ([White et al. 1999](#)).

Clinical Program for Sodium Oxybate in Fibromyalgia

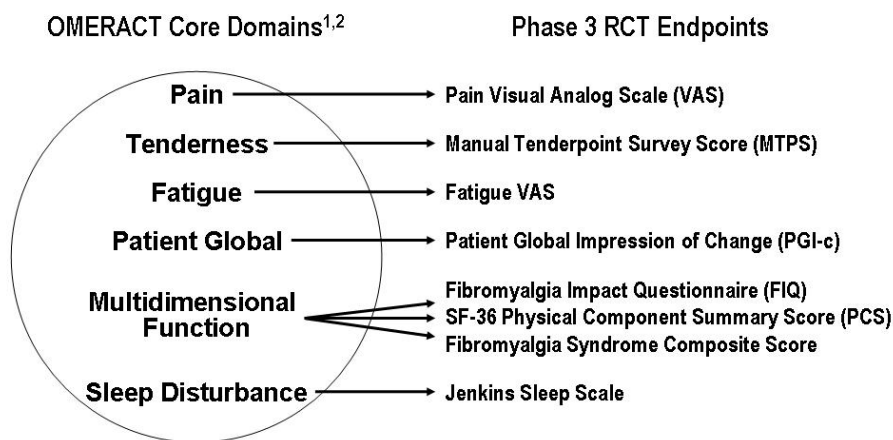
The clinical program for sodium oxybate in the treatment of fibromyalgia embodies the recommendations of OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials, now Outcome Measures in Rheumatology), an international organization that developed a consensus on the most important symptoms (core domains) that all fibromyalgia clinical trials should study. Based on a series of iterative exercises with physicians who treat fibromyalgia and patients with fibromyalgia, the OMERACT-identified core symptom domains include pain, tenderness, fatigue, patient global, multidimensional function, and sleep disturbance ([Figure A](#)). The multiple endpoints studied in the Phase 2 and Phase 3 trials

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with sodium oxybate fulfill the OMERACT recommendations and are therefore highly relevant both to physicians and patients with fibromyalgia (see [Section 4.3.2.1](#)). Pain, the hallmark symptom of fibromyalgia, was agreed upon with the FDA as the single primary endpoint for the Phase 3 trials in the clinical program for this application.

Figure A OMERACT Core Fibromyalgia Symptom Domains

Phase 3 Study Endpoints Match OMERACT Core Fibromyalgia Symptom Domains



¹ Choy, EH et al. Rheum Dis Clin N Am 35 (2009) 329–337

² Mease P, et al. J Rheumatol 2007; 34: 1415-1425.

Results from two identically designed, well-controlled pivotal Phase 3 efficacy and safety studies with sodium oxybate show robust and consistent improvement across these core symptom domains in fibromyalgia ([Table A](#) and [Section 4.3.2.4](#)). These data are both statistically significant and clinically meaningful. Sodium oxybate significantly improved pain, functionality, fatigue, changes in overall fibromyalgia condition, and disturbed sleep.

Table A. Core Symptom Domain Efficacy Results in the Phase 3 Controlled Studies

Endpoint/Domain	Study 06-008				Study 06-009			
	Placebo (N=183)	SXB 4.5 g/night (N=182)	SXB 6 g/night (N=183)	Overall p-value	Placebo (N=188)	SXB 4.5 g/night (N=195)	SXB 6 g/night (N=190)	Overall P-value
PAIN (painVAS: Primary Endpoint)								
Responder (≥30% reduction), n (%)	50 (27.3)	84 (46.2)	72 (39.3)	<0.001	38 (20.2)	69 (35.4)	67 (35.3)	0.001
p-value vs. placebo	N/A	<0.001	0.015		N/A	<0.001	0.001	
FUNCTION (FIQ Total Score)								
Responder (≥30% reduction), n (%)	55 (30.1)	84 (46.2)	72 (39.3)	0.007	41 (21.8)	77 (39.5)	76 (40.0)	<0.001
p-value vs. placebo	N/A	0.002	0.062		N/A	<0.001	<0.001	
FUNCTION (SF-36 PCS)								
Change from baseline, LS Mean (SE)	3.48 (0.611)	6.01 (0.599)	5.95 (0.599)	0.003	2.58 (0.569)	4.93 (0.564)	4.83 (0.563)	0.004
p-value vs. placebo	N/A	0.003	0.003		N/A	0.003	0.005	
FATIGUE (Fatigue VAS)								
Change from baseline, LS Mean (SE)	-15.07 (2.053)	-24.01 (2.010)	-20.96 (2.011)	0.006	-11.86 (1.927)	-20.18 (1.934)	-19.26 (1.899)	0.004
p-value vs. placebo	N/A	0.002	0.035		N/A	0.002	0.007	
OVERALL IMPROVEMENT (PGI-c)								
Responder (very much or much better), n (%)	41 (22.4)	73 (40.1)	61 (33.3)	0.001	26 (13.8)	51 (26.2)	57 (30.0)	<0.001
p-value vs. placebo	N/A	<0.001	0.020		N/A	0.003	<0.001	
SLEEP (JS Total Score)								
Change from baseline, LS Mean (SE)	-2.5 (0.43)	-4.7 (0.42)	-4.5 (0.42)	<0.001	-2.1 (0.36)	-3.4 (0.36)	-4.2 (0.36)	<0.001
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.007	<0.001	
SLEEP (FOSQ Total Score)								
Change from baseline, LS Mean (SE)	1.21 (0.235)	2.00 (0.230)	1.81 (0.230)	0.038	0.70 (0.214)	1.71 (0.212)	1.54 (0.212)	0.001
p-value vs. placebo	N/A	0.015	0.060		N/A	<0.001	0.005	
TENDERNESS (MTPS Site Scores)								
Change from baseline, LS Mean (SE)	-19.62 (2.814)	-30.91 (2.756)	-27.65 (2.757)	0.011	-10.20 (2.300)	-20.85 (2.282)	-17.06 (2.276)	0.003
p-value vs. placebo	N/A	0.003	0.036		N/A	<0.001	0.032	
COMPOSITE ENDPOINT (Fibromyalgia Syndrome Composite)								
(≥30% reduction in pain VAS, ≥30% reduction in FIQ total score, very much or much better in PGI-c), n (%)	30 (16.4)	56 (30.8)	56 (30.6)	0.002	20 (10.6)	40 (20.5)	44 (23.2)	0.004
p-value vs. placebo	N/A	0.001	0.001		N/A	0.008	0.001	

BOCF=baseline observation carried forward, CI=confidence interval, FIQ=Fibromyalgia Impact Questionnaire, FOSQ=Functional Outcomes of Sleep Questionnaire, ITT=intent-to-treat, JS=Jenkins Sleep Scale, LS=least squares, MTPS=Manual Tender Point Survey, N/A=not applicable, PCS=Physical Component Summary, PGI-c=Patient Global Impression of Change, SE=standard error, SF-36=Short Form-36, SXB=sodium oxybate, VAS=visual analog scale
Note: The endpoint for Studies 06-008 and 06-009 was Week 14.

Effects were seen as early as one week after treatment initiation and persisted throughout the two 14-week controlled trials and a 38-week open-label extension trial, for a total combined exposure of up to one year. Effects for the 4.5 and 6 g doses were similar, although the 6 g dose provided additional benefit to a subpopulation of patients with severe baseline pain (≥ 70 on the pain Visual Analog Scale). This suggests that, when warranted by individual patient need and tolerability, the 6 g dose provides an important dose option for physicians and their patients. In the Phase 3 open-label extension trial, which enrolled subjects who completed either controlled study, effectiveness was maintained at a fairly constant mean dose level of approximately 6 g (range 4.5-9 g) over the 38-week study.

These data demonstrate the broad efficacy of sodium oxybate in reducing the primary symptoms of fibromyalgia, supporting its potential as an important therapeutic option for physicians and patients with fibromyalgia.

Risks and Risk Mitigation

As with any drug treatment, there are risks associated with sodium oxybate treatment, some of which derive from properties related to its effectiveness. Clinical studies in 1060 patients with fibromyalgia and 781 patients with narcolepsy, together with postmarketing experience in more than 35,000 patients in the US (31,645 patient-years of experience), provide a significant body of data about the safety and risk profile for sodium oxybate. The nearly 8 years of postmarketing experience also provides substantial information about how the risk communication provided by the REMS program helps to mitigate these risks. The first mitigation of any pharmaceutical risk is to clearly communicate that risk to prescribers through physician labeling and to patients through the Medication Guide, both of which are carefully developed with the FDA.

The following paragraphs summarize risks currently conveyed in the proposed prescribing information for sodium oxybate for the treatment of fibromyalgia (see [Appendix A](#)). Because we have not completed the FDA review process, final language for the label has not been completed with FDA and we will work with them to finalize appropriate language for risk communication.

CNS- and Respiratory-Depressant Effects. The CNS-depressant effects of sodium oxybate have the potential to cause respiratory depression and decreases in the level of consciousness, including rare instances of coma and death, as noted in the boxed warning of the proposed product label. Among the 874 patients receiving sodium oxybate in three controlled fibromyalgia trials, isolated events of apnea, respiratory rate decreased, and hypoventilation were reported. Dyspnea with cyanosis and serious related adverse events of sleep paralysis and unresponsive to stimuli occurred in one patient after the first nightly dose and led to study discontinuation. The proposed risk mitigation for this risk focuses on the education of prescribers and patients to make them aware of the risks for CNS and respiratory depression and provide important information about the safe use of the product. Physicians will be required to certify their understanding of this information before enrolling in the REMS program. As with all drugs with central depressant effects, physicians are informed about the need to appropriately evaluate patients with compromised respiratory function who are prescribed sodium oxybate. The proposed label also includes language cautioning prescribers that sleep-disordered breathing tends to be more prevalent in obese patients and in

postmenopausal women not on hormone replacement therapy (see [Section 4.4.1.5](#), Respiratory Depression).

The proposed label also carries a boxed warning about the CNS-depressant effects of sodium oxybate and warns against the use of sodium oxybate with alcohol or CNS depressants. Among the 874 patients receiving sodium oxybate in three controlled fibromyalgia clinical trials, somnolence occurred in 3.2% and 5% of patients taking 4.5 and 6 g sodium oxybate, compared with 2.8% taking placebo. Other events potentially related to CNS depression, including depressed level of consciousness and unresponsiveness, each occurred in <1% of patients taking sodium oxybate. Events of fall and road traffic accident were low (each <1%) and similar between patients taking sodium oxybate and those taking placebo. In the proposed label and the Medication Guide, patients are warned to use extreme care while performing any task that could be dangerous or requires full mental alertness until they know whether the product has any carryover effect the next day. Patients are also warned not to engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle, for at least 6 hours after taking their second nightly dose of sodium oxybate (see [Section 4.4.1.5](#), CNS Depression).

Abuse. The proposed label has a boxed warning noting that GHB is a known drug of abuse and that abuse of GHB has been associated with important CNS adverse events. Although there were no adverse events indicative of abuse of sodium oxybate in the fibromyalgia clinical studies, the proposed REMS program addresses the potential for abuse or misuse of sodium oxybate. In addition to the established controls against diversion, abuse, and misuse that are inherent in sodium oxybate's status as a Schedule III controlled substance, the proposed REMS program summarized below and in [Section 5](#) has a tightly controlled, proven prescription and distribution process that includes verification to prevent a patient from being prescribed more than one sodium oxybate-containing product at a time and to monitor for potential abuse or misuse. The proposed label and Medication Guide instruct physicians, pharmacists, and patients about the safe use, handling, and disposal of the product; describe the risks of abuse; and state clearly that patients should not give or sell their medication to anyone else.

Suicidality and Depression. In the Phase 3 studies, a review of adverse event verbatim terms, tables and listings coded by MedDRA preferred terms, and subject diary data identified no terms consistent with adverse events related to suicidal ideation or behavior. In addition to review of adverse event terms, a more conservative method for identifying potential suicide risk was employed. The Mini International Neuropsychiatric Interview (MINI) was used at all visits as a diagnostic tool to assess participants for the presence of suicidality and Major Depression. The Beck Depression Inventory-II (BDI-II) questionnaire was also used at every visit to measure the presence and degree of depressive symptoms and also includes a question that addresses the presence of suicidal thoughts or wishes (question 9) to assess suicidality risk. This method identified 6 cases in Phase 3 trials in which subjects endorsed multiple items on these instruments and 30 cases in which subjects endorsed a single item indicating either a past history of suicidal behavior or current low level of potential suicide risk.

Among the 874 subjects taking sodium oxybate in three controlled fibromyalgia trials, adverse events of major depression and depressed mood occurred in <1% of patients, and a

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single event of depression with suicidal ideation was reported, leading to study discontinuation. In all treatment groups in the Phase 3 placebo-controlled studies, results from the MINI major depressive episode module demonstrated reductions from baseline in the number of subjects with responses indicative of a major depressive episode. Patients with fibromyalgia may have comorbid symptoms of depression which should be kept in mind during treatment with sodium oxybate.

Therefore, the proposed risk mitigation for this product focuses on the education of prescribers and patients regarding the safe and appropriate use of this product and awareness in the setting of potentially emergent depression or suicidality. The proposed label states that the emergence of depression in patients treated with sodium oxybate requires careful and immediate evaluation, and that patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking sodium oxybate (see [Section 4.4.1.5](#), Suicidality and Depression subsections).

Weight Loss. Mean body weight and body mass index decreased in patients on sodium oxybate (versus minimal increases in those on placebo) in the fibromyalgia clinical trials. Although this patient population tends to be overweight, the magnitude of decrease (mean decreases of -4.81 kg in body weight and -1.75 kg/m² in BMI at Week 52) could potentially pose a risk to an individual who is underweight at inception of therapy or who has difficulty maintaining adequate weight. The mitigation for this risk is to education physicians, pharmacists, and patients by describing the changes in body weight and BMI in the Adverse Reactions section of the proposed product label (see [Section 4.4.1.5](#), Weight Loss).

Other Adverse Events. In the Phase 2 and three Phase 3 fibromyalgia trials in 1060 sodium oxybate-treated patients, there were no deaths. Of 26 subjects reporting treatment-emergent serious adverse events (SAEs) in the Phase 2 and Phase 3 studies, six subjects reported SAEs considered related or possibly related to treatment by the investigator or the sponsor. Four of these six subjects had one or more serious adverse events (vomiting, sleep paralysis, unresponsive to stimuli, headache, and gastrointestinal hypomotility) considered related to treatment, all of which led to study discontinuation. A fifth subject had treatment-related serious adverse events of accidental overdose and encephalopathy that led to interruption of study drug dosing; the subject was restarted on study drug without incident. A sixth subject had a serious adverse event of bipolar disorder that the investigator assessed as unrelated to treatment; the sponsor could not rule out a possible relationship to treatment. The most common treatment-emergent adverse reactions (incidence $\geq 5\%$ for the All Sodium Oxybate treatment group and twice the rate seen with placebo) in the two Phase 3 controlled trials in fibromyalgia were nausea/vomiting (21.0%), vertigo/dizziness (16.1%), anxiety (6.3%), and nasal congestion/sinusitis (5.5%). For most of these events, onset was highest in the first 2 weeks after treatment initiation in the Phase 2 and Phase 3 controlled studies. After Week 2, the rates of most of the frequent adverse events in the 4.5 g, 6 g, and All Sodium Oxybate treatment groups had decreased by at least one-half. The risk mitigation for these events focuses on physician and patient education. The serious and frequent adverse events in the fibromyalgia clinical trials are described in the proposed label, as are the frequent events seen in narcolepsy clinical program and in postmarketing experience with the marketed product to provide an overall safety profile for sodium oxybate (see [Section 4.4](#)).

REMS Program for Sodium Oxybate for Fibromyalgia

The proposed REMS for sodium oxybate for fibromyalgia, paralleling the current REMS for Xyrem, is designed to clearly and effectively communicate the risks of this medication to patients, pharmacists, physicians, and caregivers while ensuring its availability to the appropriate patient population (see [Section 5](#)). In addition to physician, pharmacist, and patient education, the program includes multiple interactions with patients, providing opportunities for questions about the information they are given. The well-controlled, interactive distribution system mitigates the potential for abuse and misuse. Postmarketing experience in approximately 35,000 US patients (an estimated 31,645 patient-years of exposure) indicates a low incidence of events of CNS and respiratory depression, suicidality and depression, and abuse with this program. Other adverse events associated with sodium oxybate use in fibromyalgia studies are similar to those seen in patients with narcolepsy and can generally be managed by careful prescribing and close monitoring of individual patients and through careful pharmacovigilance.

A New Treatment Option to Meet an Ongoing Need

Although recent approvals of three fibromyalgia medications have provided some relief for patients, no product helps all patients, relieves pain completely, or addresses all the combined burdens of pain, fatigue, disturbed sleep, and loss of function. With no single treatment that addresses all the major symptoms of fibromyalgia, physicians and patients turn to a multipronged approach, with different medications to manage the several primary symptoms. This approach imposes additional complexity and inconvenience, as well as the risk of additive side effects and adverse drug reactions from a combined drug regimen. Patients with fibromyalgia need additional treatment options, including an effective therapy that can address their multiple symptoms and restore their ability to function in daily life. In the context of their ongoing need, the clinical data presented in this document are compelling.

Sodium oxybate provides a solution to the unmet needs of those patients who continue to seek broad symptom relief in spite of their current therapies, who continue to suffer pain, or who need a different tolerability profile. Sodium oxybate offers an important new therapeutic option, providing significant benefits across multiple fibromyalgia symptoms. The choice to use sodium oxybate, as with all medicines, should be made by the physician who has evaluated its potential risks to the patient and determined that the benefits for that patient outweigh the potential risks.

Without the option of sodium oxybate therapy, physicians will have fewer alternatives to offer patients whose needs are not met by, or who cannot tolerate, current therapies. Patients enduring chronic pain, fatigue, disturbed sleep, and an impaired ability to perform the simple tasks of everyday living will not have access to a medication with a unique mechanism of action that has significantly reduced all these symptoms and has been used safely in clinical trials. We believe that the magnitude and persistence of benefit for multiple symptoms of fibromyalgia clearly outweigh the product's risks, particularly as mitigated by the proposed REMS program (see [Sections 5](#) and [6](#)).

1 INTRODUCTION

1.1 Rationale for Development

Currently, sodium oxybate (under the tradename Xyrem[®] [sodium oxybate] oral solution CIII) is approved to treat excessive daytime sleepiness and cataplexy in narcolepsy in the US and various symptoms of narcolepsy in Europe and Canada.

Sodium oxybate has been developed for the treatment of fibromyalgia, a chronic disease characterized by widespread pain for at least 3 months and pain in at least 11 of 18 anatomically defined tender points (Wolfe et al. 1990). Mean baseline pain levels have been reported to range from 6.1 to 7.1 on 0 to 10 numerical rating scales or 0 to 10 visual analog scales (VAS; Arnold et al. 2004, Mease et al. 2008b). These pain levels have been shown to persist over long periods (Wolfe et al. 1997a). In addition to pain and tenderness, patients suffer a constellation of often debilitating symptoms, including fatigue, decreased ability to function in daily life, poor sleep, decreased health-related quality of life, stiffness, depression, and anxiety.

Fibromyalgia is the second most common diagnosis made by rheumatologists in the US, affecting 3 to 6 million people, with an estimated prevalence of 3.4% in women and 0.5% in men (Goldenberg 1999). It is associated with high levels of healthcare utilization and cost. A 2005 analysis of fibromyalgia-related health care costs for privately insured employees in 16 US companies (2.6 million covered lives) found that total (direct and indirect) costs among the 17,206 employees with fibromyalgia were \$10,199, nearly twice those of controls (White et al. 2008). Average total direct costs, including medical and drug costs, for employees with fibromyalgia exceeded costs for controls by 86%. Employees in the fibromyalgia sample missed an average 29.8 days, or approximately 15% of all working days in 2005, nearly 3 times the work loss among controls.

With no single treatment that addresses all the major symptoms of fibromyalgia, physicians and patients use a variety of medications to manage individual symptoms, an approach that brings additional treatment cost and inconvenience, as well as the risk of adverse drug reactions from a combined drug regimen. Patients need additional treatment options to address their multiple symptoms and restore their ability to function in daily life.

As a GABA_B- and GHB-receptor agonist, sodium oxybate exhibits a mechanism of action that is distinct from previously approved medications for the treatment of fibromyalgia. While the precise mechanism of action of sodium oxybate in fibromyalgia is unknown, it is hypothesized that sodium oxybate has direct analgesic effects through GABA_B receptor-mediated inhibition pain processing at several sites in the neuraxis including the spinal cord (Chanimov et al. 1999, Hosli et al. 1983), affecting both ascending pain transmission and descending pain inhibition (Goudet et al. 2009). Sodium oxybate, acting through GABA_B receptors, also reduces wakefulness during sleep and number of awakenings from sleep through its inhibitory actions on wake-active neurons, and increases slow-wave activity and slow-wave sleep by its inhibitory actions on thalamocortical networks (Crunelli et al. 2006; Pardi & Black 2006). It is believed that improvement of sleep may at least partly contribute to analgesia, given the established relationship between disturbed sleep and decreased pain thresholds (Moldofsky 2008).

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The benefits of sodium oxybate on multiple symptoms of fibromyalgia were first shown in two exploratory studies and in a Phase 2 controlled study demonstrating the overall safety and benefit of 4.5 and 6 g/night doses of sodium oxybate over 8 weeks in patients with fibromyalgia. The Phase 2 study also demonstrated objective changes in sleep parameters using nocturnal polysomnography (PSG), which were consistent with improvement of the sleep disturbance that is a common symptom of fibromyalgia.

Based on these findings and the results of the Phase 2 study, two identically designed Phase 3 placebo-controlled studies with sodium oxybate at doses of 4.5 and 6 g/night were conducted in a representative population of patients with fibromyalgia. These studies demonstrated the substantial benefits of sodium oxybate across multiple fibromyalgia symptom domains, including pain, functionality, fatigue, changes in overall fibromyalgia condition, and subjective sleep over 14 weeks of treatment. A Phase 3 open-label extension study open to patients completing either of the two Phase 3 controlled studies demonstrated the safety, tolerability, and long-term efficacy of sodium oxybate at doses up to 9 g/night with total exposures of up to one year. Drug-drug interaction studies were also conducted to support the clinical program in fibromyalgia (see [Section 2.4.6](#)).

This demonstrated effectiveness across multiple symptom domains, together with its unique mechanism of action, minimal interactions with drugs commonly used in treating fibromyalgia, and demonstrated safety profile in nearly 8 years of postmarketing use in approximately 35,000 US patients (31,645 patient-years), provides strong support for sodium oxybate as an important new therapeutic option for patients suffering this chronic and often debilitating disease.

Market research indicates that sodium oxybate would serve the continuing need of a modest but significant portion of the fibromyalgia patient population. Of the 3 to 6 million people in the US estimated to have fibromyalgia, approximately 1.4 million are ever correctly diagnosed. Of those patients who are diagnosed, about 90% or 1.26 million receive pharmacologic treatment. Decision Resources, an independent market analysis group estimates that sodium oxybate treatment will grow to about 6 percent of that treated patient population, or approximately 120,000 patients, at the peak year in 2018.

The proposed Risk Evaluation and Mitigation Strategy (REMS) program for sodium oxybate, paralleling the current effective risk management program for Xyrem, is designed to communicate the risks of this medication to patients, physicians, and caregivers while ensuring its availability to the appropriate patient population.

1.2 Proposed Indication and Dosage and Administration

This application seeks approval for the 4.5 and 6 g/night doses of sodium oxybate, with a proposed indication for the treatment of fibromyalgia.

The recommended doses of sodium oxybate are 4.5 and 6 g/night. The recommended starting dose is 4.5 g/night, divided into two equal doses of 2.25 g each. Based on data from the clinical program in fibromyalgia, the 4.5 g/night dose is expected to provide benefit for a substantial portion of patients. The 6 g/night dose is expected to provide additional benefit for some patients when warranted by individual patient need and tolerability. Dose can be increased in 1.5 g/night (2 x 0.75 g) increments at weekly intervals to evaluate clinical response and minimize adverse effects.

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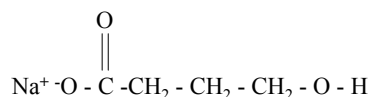
Sodium oxybate should be taken in two equal, divided doses: the first at bedtime, and the second 2.5 to 4 hours later. Both doses of sodium oxybate should be prepared before bedtime. Before ingestion, each dose should be diluted with $\frac{1}{4}$ cup (~60 mL) of water in the empty container with child-resistant cap provided. Typically patients fall asleep in ~15 minutes, although some patients have reported falling asleep more rapidly. In some instances sleep may come on abruptly (ie, without first feeling drowsy). Therefore patients should take each dose while in bed. Patients may need to set an alarm to awaken for the second dose. The second dose should be prepared before taking the first dose, and should be placed near the patient's bed. After taking each dose, patients should lie down in bed.

2 CHEMISTRY, PHARMACOLOGY, TOXICOLOGY, AND PHARMACOKINETICS

The chemistry, pharmacology, toxicology, and pharmacokinetics (PK) of sodium oxybate have been described in the literature and in regulatory submissions to support Xyrem, the sodium oxybate product currently to treat various symptoms of narcolepsy. Aside from three clinical drug-drug interaction studies to support development of sodium oxybate for treatment of fibromyalgia, the most clinically relevant findings in these areas have been summarized in the approved labeling and pending labeling supplements for Xyrem.

2.1 Chemistry

Sodium oxybate is the sodium salt of GHB. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$, and the molecular weight is 126.09 g/mole. The chemical structure is:



Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions.

2.2 Pharmacology and Receptor Binding

At pharmacologic concentrations (doses ≥ 2 -3 g), sodium oxybate acts as an agonist at both GHB and GABA_B receptors, causing several pharmacological and behavioral effects, including effects on sleep ([Lingenhoehl et al. 1999](#), [Maitre 1997](#), [Mathivet et al. 1997](#)). Accumulated evidence suggests that most observed behavioral effects of pharmacological concentrations of sodium oxybate, including effects on sleep, are mediated through GABA_B receptors ([Pardi & Black 2006](#), [Maitre 1997](#)).

While the precise mechanism of action of sodium oxybate in fibromyalgia is unknown, it is hypothesized that sodium oxybate has direct analgesic effects through GABA_B receptor-mediated inhibition pain processing at several sites in the neuraxis including the spinal cord ([Chanimov et al. 1999](#), [Hosli et al. 1983](#)), affecting both ascending pain transmission and descending pain inhibition ([Goudet et al. 2009](#)). Sodium oxybate, acting through GABA_B receptors, also reduces wakefulness during sleep and number of awakenings from sleep through its inhibitory actions on wake-active neurons, and increases slow-wave activity and slow-wave sleep by its inhibitory actions on thalamocortical networks ([Crunelli et al. 2006](#), [Pardi & Black 2006](#)). It is believed that improvement of sleep may at least partly contribute to analgesia, given the established relationship between disturbed sleep and decreased pain thresholds ([Moldofsky 2008](#)).

2.3 Nonclinical Development Program

The nonclinical toxicology program supporting the 2002 approval of Xyrem (sodium oxybate) oral solution encompassed a complete spectrum of toxicity, reproduction, teratology, and mutagenicity studies. Results of these studies support its safe use in humans at the recommended doses and in the proposed dosing regimen. A carcinogenicity assessment of sodium oxybate did not show tumor-producing potential.

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As agreed in the 27 February 2006 End-of-Phase 2 meeting with the FDA, no new nonclinical studies were required for this application.

2.4 Clinical Pharmacokinetics

Following oral administration, sodium oxybate is absorbed rapidly and consistently across the clinical dose range, with an absolute bioavailability of 88%. The average peak plasma concentrations (1st and 2nd peak) following administration of a 4.5 g total daily dose, divided into two equivalent doses given under fasting conditions 4 hours apart, were similar: 84 and 93 micrograms/milliliter (mcg/mL), respectively. The average time to peak plasma concentration (T_{max}) ranged from 0.5 to 1.25 hours in eight pharmacokinetic studies. Following oral administration, the plasma levels of sodium oxybate increase more than proportionally with increasing dose, with blood levels increasing 3.7-fold as dose is doubled from 4.5 to 9 g. Administration of sodium oxybate immediately after a high-fat meal resulted in delayed absorption (average T_{max} increased from 0.75 h to 2.0 h) and reductions in peak plasma level (C_{max}) by a mean of 58% and systemic exposure (AUC) by a mean of 37%. Therefore patients should allow at least 2 hours after eating before taking the first dose of sodium oxybate. Pharmacokinetics are not altered with repeat dosing. In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate following a single oral dose of 4.5 g. The half-life is typically 0.5 to 1 hour.

2.4.1 Distribution

Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190 to 384 mL/kg. At sodium oxybate concentrations ranging from 3 to 300 mcg/mL, less than 1% is bound to plasma proteins.

2.4.2 Metabolism

Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. The primary pathway involves a cytosolic NADP⁺-linked enzyme, GHB dehydrogenase, which catalyzes the conversion of sodium oxybate to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyzes the conversion to succinic semialdehyde in the presence of α -ketoglutarate. An alternate pathway of biotransformation involves β -oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

2.4.3 Elimination

The clearance of sodium oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. The half-life is typically 0.5 to 1 hour. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible.

2.4.4 Renal Disease

Because the kidney does not have a significant role in the excretion of sodium oxybate, no pharmacokinetic study in patients with renal dysfunction has been conducted; no effect of renal function on sodium oxybate pharmacokinetics would be expected.

2.4.5 Hepatic Disease

Results of the absolute bioavailability study show little first-pass metabolism. The kinetics of sodium oxybate in 16 cirrhotic patients, half without ascites (Child's Class A) and half with ascites (Child's Class C), were compared to the kinetics in 8 healthy adults after a single oral dose of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 mL/min/kg in healthy adults to 4.5 and 4.1 mL/min/kg in Class A and Class C patients, respectively. Elimination half-life ($t_{1/2}$) was significantly longer in Class C and Class A patients than in control subjects (mean $t_{1/2}$ of 59 and 32 minutes, respectively, versus 22 minutes). It is prudent to reduce the starting dose of sodium oxybate by one-half in patients with liver dysfunction.

2.4.6 Drug-Drug Interaction

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 mcg/mL). These levels are considerably higher than levels achieved at therapeutic doses. Consistent with the *in vitro* data on CYPs and a metabolic path involving the Krebs cycle, drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. However, pharmacodynamic (PD) interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in oxybate kinetics. Drug interaction studies to support the clinical program for fibromyalgia showed no pharmacokinetic or significant pharmacodynamic interactions with duloxetine, tramadol, or lorazepam. See [Section 4.2](#) for additional details.

3 PHARMACODYNAMICS AND PROPOSED MECHANISM OF ACTION IN FIBROMYALGIA

As a GABA_B- and GHB-receptor agonist, sodium oxybate exhibits a mechanism of action that is distinct from previously approved medications for the treatment of fibromyalgia. Sodium oxybate is a sodium salt of gamma hydroxybutyrate (GHB), which is endogenously synthesized from the inhibitory neurotransmitter GABA, present in micromolar quantities in the brain, and functions as a neurotransmitter with specific localization in neurons, specific receptors, and specific uptake mechanisms (Maitre 1997). GHB, the active constituent of sodium oxybate, binds with high affinity to GHB-specific receptors (Maitre 1997) and lower affinity to GABA_B receptors (Lingenhoehl et al. 1999, Mathivet et al. 1997).

It is hypothesized that the majority of pharmacological effects of sodium oxybate are mediated through the GABA_B receptor, based on evidence in animal studies showing a lack of pharmacological effects of GHB in mice lacking functional GABA_B receptors (Kaupmann et al. 2003), and loss of *in vitro* electrophysiological effects following blockade of GABA_B receptors with specific GABA_B antagonists (Crunelli et al. 2006).

GABA_B receptors play an integral and complex role in pain control. GABA_B receptors are enriched in pain processing regions including the dorsal root ganglia, spinal cord, medulla, and higher pain control networks (Goudet et al. 2009), and GABA_Bergic activity is analgesic at several sites (Goudet et al. 2009). GABA_Bergic agents act both postsynaptically and presynaptically. For example, stimulation of GABA_B receptors located presynaptically on the terminals of nociceptive primary afferent neurons reduces the release of the pro-nociceptive neurotransmitters glutamate and substance P (Malcangio & Bowery 1993). Animal studies show that the effects of GHB are consistent with GABA_B receptor-mediated analgesia (Chanimov et al. 1999, Hosli et al. 1983, Sherman & Gebhart 1975). Since GABA_Bergic transmission has been found to be diminished in animal models of chronic pain, sodium oxybate administration may ameliorate a similar GABA_Bergic pathology in fibromyalgia patients.

Other actions of GHB may directly or indirectly affect pain and other fibromyalgia symptoms. In animal studies, at pharmacological doses, GHB inhibits dopamine and norepinephrine neurons; this inhibition is followed by a rebound increase in neurotransmitter level and/or neuronal activity (Pardi & Black 2006). Restoration of dopamine and norepinephrine would be hypothesized to enhance endogenous pain inhibition and relieve fibromyalgia pain. A similar reduction of cholinergic transmission and increased storage of acetylcholine has been demonstrated following GHB administration in animal studies (Pardi & Black 2006), and in addition, histamine neurons are inhibited by GABA_Bergic activation (Stevens et al. 1999).

These inhibitory actions may underly GHB's effects on sleep. Current hypotheses indicate that sleep and waking are regulated by reciprocal interactions between "wake-active" brain regions (including dopamine, norepinephrine, serotonin, and histamine neurons) and "sleep-active" regions (GABAergic neurons in the anterior hypothalamus) (Saper et al. 2001). GABA_Bergic inhibition of wake-active regions may result in decreased awakenings during sleep and may result in restored neurotransmitter levels the next day (Pardi & Black 2006). In addition, GABA_Bergic effects in the thalamus are hypothesized to increase slow-wave

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oscillations and deep (slow-wave) sleep ([Crunelli et al 2006](#)). The effects of sodium oxybate on sleep, including decreased wakefulness after sleep onset, decreased number of awakenings from sleep, and increased slow-wave sleep have been demonstrated in fibromyalgia patients, narcolepsy patients, other clinical populations, and healthy subjects.

It is hypothesized that treatment of sleep disturbance in fibromyalgia may contribute to improvement of pain, given the relationship between disturbed sleep and next-day pain demonstrated in a number of studies ([Moldofsky 2008](#)). Furthermore, statistical path analyses have concluded that in fibromyalgia patients, increased sleep disturbance predicted increased pain, which in turn predicted poorer physical functioning and subsequently greater depression ([Bigatti et al. 2008](#)).

Sodium oxybate's effects on fibromyalgia symptoms are hypothesized to occur through different mechanisms of action than those of currently approved fibromyalgia products. Pregabalin is thought to diminish pain transmission primarily via actions at the alpha-2-delta subunit of voltage sensitive calcium channels resulting in reduction of calcium-dependent neurotransmitter release in the ascending pain pathway ([Dooley et al. 2007](#)) and the two serotonin and norepinephrine reuptake inhibitors [SNRIs], duloxetine and milnacipran, are thought to reduce pain primarily through inhibition of serotonin and norepinephrine reuptake, thereby enhancing serotonergic and noradrenergic descending pain inhibitory pathways ([Mease 2009](#)). Sodium oxybate does not bind to the alpha-2-delta subunit of voltage sensitive calcium channel or at serotonin or norepinephrine transporters.

4 CLINICAL DEVELOPMENT PROGRAM

4.1 Overview

The clinical development program for fibromyalgia, building on past experience from sodium oxybate nonclinical, clinical pharmacology, and clinical safety studies, included a total of seven studies. Four studies were conducted in subjects with fibromyalgia: one Phase 2, placebo-controlled safety and efficacy study (OMC-SXB-26), two Phase 3 placebo-controlled safety and efficacy studies (06-008 and 06-009), and one Phase 3 open-label extension study (06-010, performed in subjects who completed either 06-008 or 06-009). Three pharmacokinetic drug-drug interaction studies were conducted in healthy volunteers to evaluate sodium oxybate with drugs from three classes that are commonly used in this patient population, including the antidepressant duloxetine hydrochloride, the benzodiazepine lorazepam, and the opioid tramadol. At the time of the four-month safety update for this application, Study 06-010 was ongoing; safety data are from an interim analysis database. Efficacy data are as of the original NDA.

4.2 Summary of Drug Interaction Studies

Three Phase 1 studies characterized the pharmacodynamics and pharmacokinetics of sodium oxybate with lorazepam, tramadol, and duloxetine in healthy subjects. Lorazepam was selected as representative of benzodiazepines as it is one of the most common benzodiazepines used for the treatment of anxiety or insomnia associated with anxiety in fibromyalgia patients. Tramadol is a centrally acting synthetic opioid commonly used for the treatment of chronic pain in fibromyalgia. Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) commonly used for the treatment of depression and generalized anxiety disorder (GAD) and approved for treatment of fibromyalgia in June 2008.

4.2.1 Study Designs

As sodium oxybate does not inhibit CYP enzymes, and there are no known enzymes common to the metabolic paths of sodium oxybate and any of the co-administered drugs, pharmacokinetic interactions were not anticipated. However, since sodium oxybate, lorazepam, and tramadol have been independently associated with sedation and CNS depression, the doses and study designs were optimized for pharmacodynamic assessment, while maintaining safety for study subjects.

A single 2.25 g dose of sodium oxybate (SXB) was used in all three studies, since this represents the first dose of the two-dose regimen used to achieve the lower (4.5 g/night) of the two doses studied in the placebo controlled Phase 3 efficacy studies. Because of the short $t_{1/2}$ of sodium oxybate, PK measurements taken after the first dose are very similar to those taken after the second dose (kinetically, the two 2.25 g doses used to achieve the 4.5 g dose can be considered as two single doses). Thus, it was sufficient to evaluate the PK and PD interactions with one dose of sodium oxybate in these studies.

The study designs were similar for the lorazepam and tramadol studies, and utilized placebo for sodium oxybate as well as for the co-administered drug, such that the treatment regimens included SXB + other drug, SXB placebo + other drug, and SXB + other drug placebo. Subjects were randomized to one of the treatment regimens for each of three study periods,

according to a double-blind complete crossover design, with a 3-day washout between periods.

For lorazepam, a single 2 mg dose was selected because this dose is recommended as the initial dose for treating insomnia associated with anxiety. Tramadol was dosed 100 mg per day for 5 days using an extended-release formulation, as 100 mg is the starting dose, the drug is often administered chronically, and 5 days is sufficient to ensure that pharmacokinetic steady-state is achieved.

The design for the duloxetine study varied slightly and did not use a duloxetine placebo. Single 2.25 g doses of sodium oxybate or sodium oxybate placebo were dosed according to a double-blind crossover design 1 to 4 days before dosing with duloxetine and then again in the same way (double-blind, crossover) on Days 5 and 8 of an 8-day regimen of duloxetine 60 mg/day (the approved dose for fibromyalgia).

Blood sampling at pre-defined time points enabled estimation of PK parameters for drugs administered alone and in combination. Assessment of PD interactions at pre-defined time points included subject self-assessment of sleepiness/alertness (100 mm VAS; 0=very alert to 100=very sleepy) and the Digit Symbol Substitution Test (DSST) for cognition and attention. Tolerability was evaluated based on the occurrence of adverse events (AEs), vital signs, physical examination, and laboratory and clinical tests, including 12-lead electrocardiograms.

4.2.2 Pharmacokinetic Results

The pharmacokinetics of each drug was consistent with their established profiles; no substantial changes were observed for any of the drugs when administered in combination. Mean pharmacokinetic parameters for drug exposure (C_{max} and AUC) and statistical comparisons for these parameters for combination versus single-agent administration are given in Table 1, [Table 2](#), and [Table 3](#).

Table 1. Pharmacokinetic Parameters for Sodium Oxybate and Lorazepam When Dosed Alone and in Combination

Analyte	Parameter (Units)	N	Mean* during co-administration	Mean* during Single-Agent Dosing	Ratio of Means* (%): Coadministration /Single-Agent Dosing	90% Confidence Interval	Regimen P-value
SXB	C_{max} (ug/mL)	18	84.3	77.3	109.02	98.51-120.65	0.16
SXB	AUC_{0-t} (ug•h/mL)	18	96.8	90.8	106.60	93.68-121.31	0.40
SXB	AUC_{0-inf} (ug•h/mL)	18	97.1	91.0	106.67	93.75-121.37	0.39
LRZ	C_{max} (ng/mL)	18	32.6	34.3	95.03	87.29-103.45	0.31
LRZ	AUC_{0-t} (ng•h/mL)	18	521.7	533.4	97.81	94.48-101.26	0.28
LRZ	AUC_{0-inf} (ng•h/mL)	18	597.3	605.5	98.65	94.78-102.67	0.56

Table 2. Pharmacokinetic Parameters for Sodium Oxybate, Tramadol, and Tramadol M1 Metabolite (O-desmethyltramadol) When Dosed Alone and in Combination

Analyte	Parameter (Units)	N	Mean* during Co-administration	Mean* during Single-Agent Dosing	Ratio of Means* (%): Coadministration /Single-Agent Dosing	90% Confidence Interval	Regimen P-value
SXB	C _{max} (ug/mL)	17	42.1	41.6	101.26	78.38-130.83	0.9324
SXB	AUC _{0-t} (ug•h/mL)	17	66.7	64.5	103.29	88.68-120.31	0.7141
SXB	AUC _{0-inf} (ug•h/mL)	17	66.9	64.8	103.31	88.74-120.28	0.7115
TRM	C _{maxss} (ug/mL)	17	190.0	166.2	114.30	100.42-130.08	0.0904
TRM	AUC ₀₋₂₄ (ug•h/mL)	17	3190.1	2803.6	113.79	96.32-134.42	0.1937
M1-TRM	C _{maxss} (ug/mL)	17	51.1	45.9	111.20	95.57-129.40	0.2375
M1-TRM	AUC ₀₋₂₄ (ug•h/mL)	17	909.3	814.0	111.71	94.22-132.45	0.2713

* Geometric mean

SXB=Sodium oxybate, TRM=Tramadol, M1-TRM=tramadol metabolite (O-desmethyltramadol)

Source: 07-008 CSR Tables 15.2.1.13, 15.2.1.14, and 15.2.1.15

Table 3. Pharmacokinetic Parameters for Sodium Oxybate and Duloxetine When Dosed Alone and in Combination

Analyte	Parameter (Units)	N	Mean* during Co-administration	Mean* during Single-Agent Dosing	Ratio of Means* (%): Coadministration /Single-Agent Dosing	90% Confidence Interval	Regimen P-value
SXB	C _{max} (ug/mL)	24	44.2	47.5	93.11	84.51-102.59	0.22
SXB	AUC _{0-t} (ug•h/mL)	24	85.5	83.4	102.60	96.72-108.83	0.46
SXB	AUC _{0-inf} (ug•h/mL)	24	85.9	83.6	102.67	96.83-108.85	0.45
DLX	C _{maxss} (ng/mL)	24	96.4	98.3	98.07	91.67-104.91	0.62
DLX	AUC ₀₋₂₄ (ng•h/mL)	24	1280.6	1286.9	99.51	96.09-103.05	0.81

* Geometric mean

SXB=Sodium oxybate, DLX= Duloxetine

Source: 07-005 CSR Tables 15.2.1.10 and 15.2.1.11

4.2.3 Pharmacodynamics

The pharmacodynamics paralleled the PK profile of individual drugs. Tramadol (TRM) alone and duloxetine (DLX) alone resulted in minimal changes in sleepiness VAS scores over time, while SXB+ DLX and SXB+TRM resulted in increases in sleepiness VAS scores that were similar to SXB alone. When administered independently, sodium oxybate and lorazepam both increased sleepiness as indicated by higher VAS scores relative to predose values. On

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average, sleepiness peaked earlier with SXB (1.5 hours) than with lorazepam (4 hours) and declined more rapidly. When the two drugs were co-administered, sleepiness VAS scores were higher than when the drugs were administered individually, and had a later and more prolonged peak than with sodium oxybate alone. Sleepiness VAS scores over time are shown in Figure 1, Figure 2, and Figure 3.

Figure 1. Sleepiness VAS for Sodium Oxybate and Lorazepam Dosed Alone and in Combination

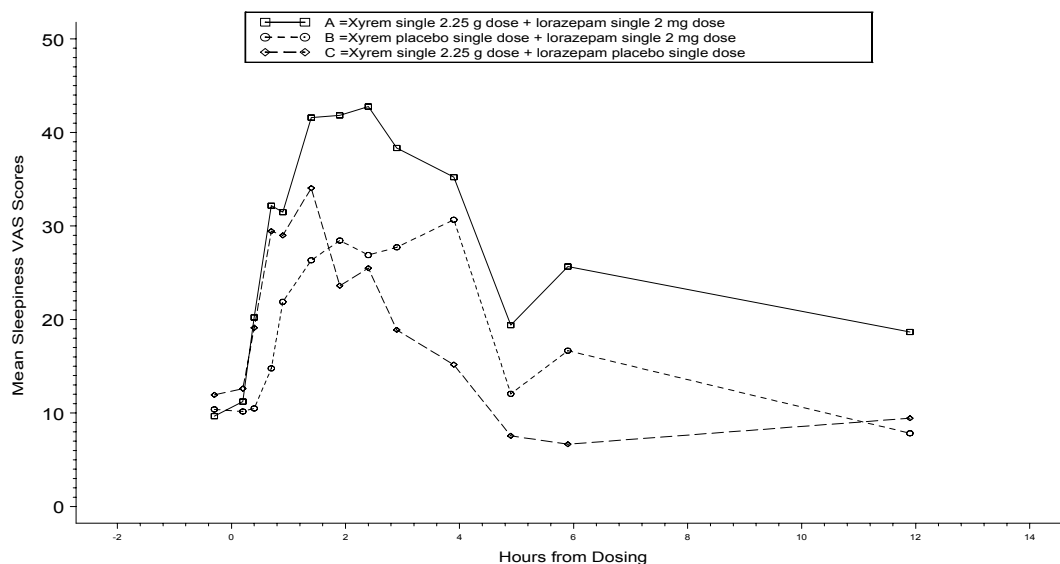


Figure 2. Sleepiness VAS Scores for Sodium Oxybate and Tramadol Dosed Alone and in Combination

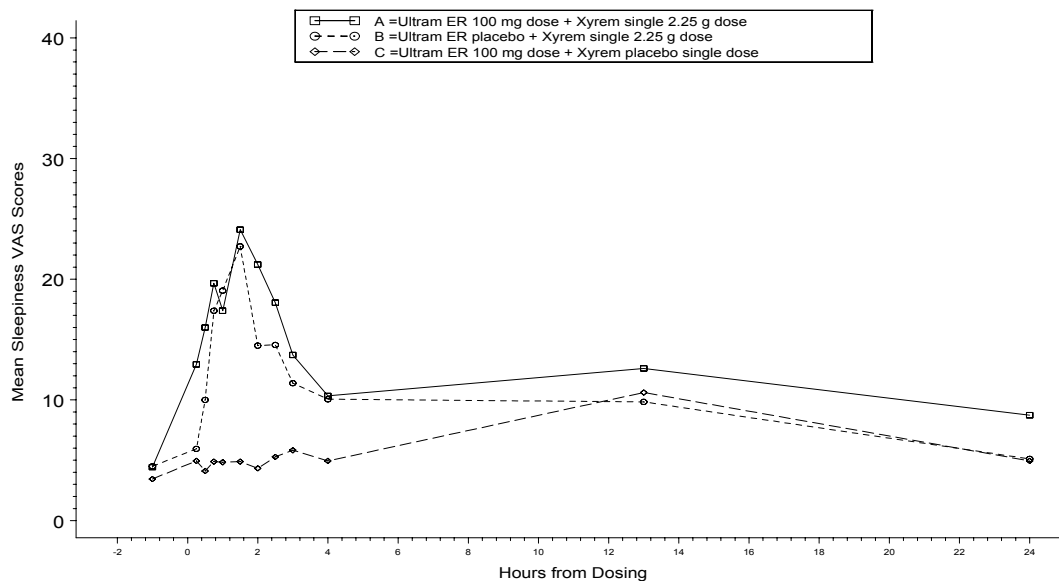
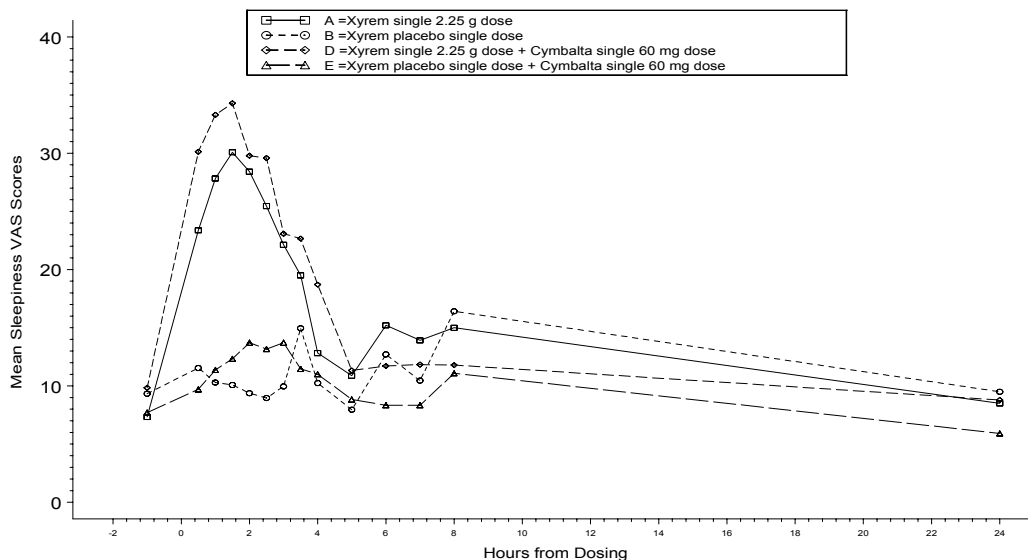


Figure 3. Sleepiness VAS Scores for Sodium Oxybate and Duloxetine Dosed Alone and in Combination



Changes in DSST scores were less sensitive to drug effect than sleepiness VAS. Compared to administration of the single agents, decreases in DSST scores with co-administration were only consistently seen with SXB+DLX (generally significant across time points versus DLX alone, and significant versus SXB alone at 1.5 h only).

Combination therapy did not increase the incidence or severity of AEs above that of individual drugs; all AEs were mild to moderate, and the only discontinuation was not related to study medication. The most common AEs reported with SXB were somnolence, dizziness, nausea, and headache.

The results of these drug interaction studies are consistent with previously reported Phase 1 drug-interaction studies indicating that sodium oxybate does not have pharmacokinetic interactions with protriptyline hydrochloride, zolpidem tartrate, modafinil, and omeprazole.

4.3 Summary of Phase 2 and 3 Studies

This summary presents a critical analysis of clinical data from one Phase 2 and three Phase 3 studies in establishing the efficacy of sodium oxybate in subjects with fibromyalgia. The Phase 2 study (OMC-SXB-26) and two of the Phase 3 studies (06-008 and 06-009) were randomized, double-blind, parallel-group, placebo-controlled trials in which the efficacy and safety of two dose levels of sodium oxybate (4.5 g/night and 6 g/night) were compared with placebo in subjects who met the 1990 American College of Rheumatology (ACR) criteria for fibromyalgia. In addition, this summary includes efficacy data from 245 subjects who completed either of the two Phase 3 controlled trials, rolled over into the Phase 3 open-label extension study (06-010), and either completed or discontinued Study 06-010 as of the interim data cutoff for data presented in the NDA. Data that were included in the ISS 4-month update from Study 06-010 for all treated patients (n=560), including ongoing patients, are presented for summaries of exposure and safety data (n=139 subjects with ≥ 26 weeks of exposure and n=76 subjects with ≥ 52 weeks of exposure including prior study exposure). No studies were prematurely terminated, nor were there any studies whose data are deemed irrelevant. [Table 4](#) presents an overview of the study designs for these Phase 2 and 3 studies.

Across all four Phase 2 and 3 studies, sodium oxybate provided clinically important therapeutic benefits across multiple domains relevant to the assessment of fibromyalgia ([Mease et al. 2007](#), [Bennett et al. 2007](#)). Sodium oxybate 4.5 and 6 g/night reduced pain and fatigue, and improved functionality and sleep in subjects with fibromyalgia. Effects were seen as early as one week after treatment initiation and persisted throughout 14-week controlled trials and the 38-week open-label trial. These results, demonstrated by both baseline observation carried forward (BOCF) and last observation carried forward (LOCF) analyses and by multiple measures for each domain, confirm and extend the results of previous work with sodium oxybate in fibromyalgia ([Scharf et al. 1998a](#) and [2003](#)).

Results from objective sleep measurements used in the Phase 2 study are consistent with the known effects of sodium oxybate on sleep architecture and the improvement in sleep-related symptoms across several significant fibromyalgia domains. This is important because sleep regulates a variety of physiological processes; slow-wave sleep, in particular, is thought to be restorative, and is associated with decreased sympathetic and cardiovascular activation as well as regulation of hormones, notably growth hormone. Chronic sleep disturbance,

commonly reported in fibromyalgia, may disrupt these processes and result in the pathology of fibromyalgia. Therefore, improving sleep continuity may restore physiology to a more normal state. In addition, pain is known to disrupt sleep; therefore, the relationship between sleep and pain is bidirectional and complex. Thus, the improvements seen in sleep, fatigue, and functioning in the Phase 3 trials may be explained in part by the improvements seen on objective sleep measures in the Phase 2 study.

Table 4. Description of Clinical Safety and Efficacy Studies

Study ID/ No. Study Centers	Total Subject Enrollment/ Enrollment goal	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	No. of Subjects by Arm Entered/ Completed	Duration of Treatment
OMC-SXB-26/ 21 in the US	195 randomized/ 150 planned	Phase 2, randomized double-blind, placebo- controlled, parallel- group	Sodium oxybate (SXB) 4.5 or 6 g/night taken orally in 2 equal divided doses Placebo solution taken orally in 2 equal divided doses	To evaluate the safety and efficacy of SXB for treatment of the symptoms of fibromyalgia in a randomized, double-blind, parallel-group, placebo-controlled trial	4.5 g/night: 62 randomized; 51 completed. 6 g/night: 67 randomized; 46 completed. Placebo: 66 randomized; 54 completed.	8 weeks
06-008/ 74 in the US	548 randomized/ 525 planned	Phase 3, randomized, double-blind, placebo- controlled, parallel- group	SXB 4.5 or 6 g/night taken orally in 2 equal divided doses SXB 4.5 g/night taken for 14 weeks SXB 6 g/night taken for 12 weeks after 2 weeks at 4.5 g/night Placebo solution taken orally in 2 equal divided doses	To evaluate the efficacy and safety of SXB at 4.5 or 6 g/night versus placebo for the treatment of fibromyalgia in a randomized, double-blind, placebo-controlled, parallel-group trial	4.5 g/night: 182 randomized; 119 completed. 6 g/night: 183 randomized; 104 completed. Placebo: 183 randomized; 111 completed.	14 weeks
06-009/ 108 total (67 in the US and 41 in Europe)	573 randomized 525 planned	Phase 3, randomized, double-blind, placebo- controlled, parallel- group	SXB 4.5 or 6 g/night taken orally in 2 equal divided doses SXB 4.5 g/night taken for 14 weeks SXB 6 g/night taken for 12 weeks after 2 weeks at 4.5 g/night Placebo solution taken orally in 2 equal divided doses	To evaluate the efficacy and safety of SXB at 4.5 or 6 g/night versus placebo for the treatment of fibromyalgia in a randomized, double-blind, placebo-controlled, parallel-group trial	4.5 g/night: 195 randomized; 129 completed. 6 g/night: 190 randomized; 116 completed. Placebo: 188 randomized; 131 completed.	14 weeks
06-010/ 115 total 74 sites included in the interim report (cutoff 02 DEC 2008) 73 in the US and 1 in Europe	245 treated and completed or discontinued as of cutoff date for interim report 02 DEC 2008 560 ultimately treated	Long-term, open- label, study	SXB 4.5, 6, 7.5 or 9 g/night taken orally in 2 divided doses	To assess the safety of SXB in long-term use (up to 38 weeks) in subjects completing a double- blind controlled trial of SXB for the treatment of fibromyalgia. To evaluate the long-term efficacy of open-label SXB in subjects with fibromyalgia and to assess the long-term effects of open-label SXB on quality of life, social and occupational functioning, and daytime fatigue in subjects with fibromyalgia	Interim data as of 02 DEC 2008 245 treated 107 completed	Up to 38 weeks

4.3.1 Summary of the Phase 2 Controlled Study (OMC-SXB-26)

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTI-CENTER TRIAL COMPARING THE EFFECTS OF ORALLY ADMINISTERED SODIUM OXYBATE WITH PLACEBO FOR THE TREATMENT OF FIBROMYALGIA

4.3.1.1 Study Design: Phase 2 Controlled Study (OMC-SXB-26)

The Phase 2 controlled study, OMC-SXB-26, evaluated sodium oxybate oral solution (4.5 and 6 g/night) in subjects with fibromyalgia. In this randomized, double-blind, placebo-controlled, parallel-group study, subjects who met the eligibility criteria underwent a drug withdrawal and washout period followed by a 2-week baseline period. Subjects who continued to meet inclusion/exclusion criteria (detailed in [Appendix B](#)), and who reported an average pain score above 4 (on a visual analog scale [VAS] of 0-10) during the last week of the baseline period were randomized 1:1:1 to receive sodium oxybate 4.5 g/night, sodium oxybate 6 g/night, or placebo in two equally divided doses each night for 8 weeks.

The primary efficacy parameter was the Fibromyalgia Syndrome Composite Response analyzed at Week 8. The Fibromyalgia Syndrome Composite Response was the proportion of subjects who achieved a reduction in average pain (by pain VAS) of $\geq 20\%$ from baseline, a reduction of $\geq 20\%$ in Fibromyalgia Impact Questionnaire (FIQ) total score from baseline, and a response of “very much better” or “much better” on the Patient Global Impression of Change (PGI-c). LOCF was the primary imputation method.

Secondary efficacy parameters included pain severity, FIQ total score and subscale scores, the proportion of FIQ responders, PGI-c, Epworth Sleepiness Scale (ESS), Sleep Patterns (Jenkins Sleep Scale [JS]), fatigue VAS, Functional Outcomes of Sleep Questionnaire (FOSQ), and Short Form-36 Physical Component Summary (SF-36 PCS). These measures are described in [Appendix C](#). In addition, objective sleep quality was measured with nocturnal polysomnography (PSG).

Safety was assessed throughout the study by the incidence of study AEs and changes in physical examination findings, ECGs, clinical laboratory tests, and vital sign measurements.

4.3.1.2 Disposition: Phase 2 Controlled Study (OMC-SXB-26)

A total of 195 subjects were randomized, 192 were treated, and 151 completed the study. [Table 5](#) presents a summary of subject disposition.

Table 5. Summary of Subject Disposition, Phase 2 Placebo-Controlled Study

Disposition	Placebo n (%)	Sodium Oxybate		Total n (%)
		4.5 g/night n (%)	6 g/night n (%)	
No. of subjects randomized	66	62	67	195
No. of subjects treated	65 (98.5)	60 (96.8)	67 (100)	192 (98.5)
No. of subjects discontinued from the study	12 (18.2)	11 (17.7)	21 (31.3)	44 (22.6)
Adverse event	3 (4.5)	6 (9.7)	14 (20.9)	23 (11.8)
Lost to follow-up	0	1 (1.6)	1 (1.5)	2 (1.0)
Non-compliance	1 (1.5)	0	0	1 (0.5)
Protocol deviation/violation	0	0	2 (3.0)	2 (1.0)
Screen failure	1 (1.5)	1 (1.6)	0	2 (1.0)
Other	7 (10.6)	3 (4.8)	4 (6.0)	14 (7.2)
No. of subjects who completed the study	54 (81.8)	51 (82.3)	46 (68.7)	151 (77.4)

Note: No. = number

Source: Table 15.1.1.2 in the OMC-SXB-26 final report

4.3.1.3 Demographics and Baseline Characteristics: Phase 2 Controlled Study (OMC-SXB-26)

The Phase 2 study population was representative of the fibromyalgia patient population described in the literature, which is primarily female, middle-aged, and overweight, with a history of fibromyalgia symptoms spanning many years.

[Table 6](#) summarizes subject demographic and baseline characteristics for the Phase 2 study. Overall, subjects were predominantly female, Caucasian, and overweight, with a mean age of 46.5 years. The mean time since first fibromyalgia symptoms and mean time since first fibromyalgia diagnosis were approximately 11 and 6 years, respectively.

Table 6. Summary of Demographic and Baseline Characteristics, Phase 2 Placebo-Controlled Study

Characteristic	Placebo (n=66)	Sodium Oxybate		Total (n=195)
		4.5 g/night (n=62)	6 g/night (n=67)	
Age (years)				
Mean (SD)	47.2 (10.69)	47.2 (11.89)	45.1 (11.51)	46.5 (11.35)
Sex – n (%)				
Female	62 (93.9)	58 (93.5)	64 (95.5)	184 (94.4)
Race				
Caucasian	59 (89.4)	56 (90.3)	65 (97.0)	180 (92.3)
Body Mass Index (kg/m²)				
N	65	61	64	190
Mean (SD)	29.41 (6.843)	30.44 (8.278)	30.64 (7.295)	30.15 (7.459)
Median	28.70	28.10	29.00	28.75
Range	19.0-46.8	18.6-56.3	18.1-50.0	18.1-56.3
Time since 1st fibromyalgia symptoms (years)				
N	65	59	64	188
Mean (SD)	11.4 (8.08)	9.9 (8.42)	10.3 (8.77)	10.6 (8.40)
Time since 1st fibromyalgia diagnosis (years)				
N	65	61	62	188
Mean (SD)	7.0 (6.84)	5.5 (5.72)	5.5 (5.33)	6.0 (6.02)

Source: Table 15.1.3 in the OMC-SXB-26 final report

4.3.1.4 Phase 2 Controlled Study Results (OMC-SXB-26)

EFFICACY

The primary efficacy parameter was the Fibromyalgia Syndrome Composite Response (the proportion of subjects who achieved a reduction in average pain [by pain VAS] of $\geq 20\%$ from baseline, a reduction of $\geq 20\%$ in FIQ total score from baseline, and a response of “very much better” or “much better” on the PGI-c) analyzed at Week 8 by LOCF. While approximately twice as many subjects on each active dose versus placebo met these criteria, the overall treatment effect approached but did not reach statistical significance ($p=0.052$). Similar results were seen for the Fibromyalgia Syndrome Composite when a $\geq 30\%$ reduction in pain VAS and FIQ was used (Table 7).

Table 7. Fibromyalgia Syndrome Composite Using $\geq 20\%$ (Primary Efficacy Endpoint) and $\geq 30\%$ Reduction (Week 8) (ITT Population, LOCF)

Efficacy Measure	Placebo (n=66)	Sodium oxybate		Overall P value
		4.5 g/night (n=62)	6 g/night (n=67)	
Fibromyalgia Syndrome Composite ($\geq 20\%$)^a				
Responders, n (%)	8 (12.9)	17 (29.8)	18 (28.1)	0.052 ^c
Fibromyalgia Syndrome Composite ($\geq 30\%$)^b				
Responders, n (%)	7 (11.3)	15 (26.3)	17 (26.6)	0.060 ^c

^a Responders were subjects who achieved $\geq 20\%$ reduction in pain VAS from baseline, $\geq 20\%$ reduction in FIQ total score from baseline, and a PGI-c response of 'very much better' or 'much better'

^b Responders were subjects who achieved $\geq 30\%$ reduction in pain VAS from baseline, $\geq 30\%$ reduction in FIQ total score from baseline, and a PGI-c response of 'very much better' or 'much better'

^c P-values are obtained from a chi-square test.

Source: OMC-SXB-26 CSR Table 15.2.1.1

An analysis using the primary efficacy parameter and statistical methods originally planned for use in the Phase 3 trials (BOCF, ITT population, $\geq 30\%$ reduction in pain VAS and FIQ, and a PGI-c of "much better" or "very much better") was also performed. In this analysis, the response with the 6 g/night dose was significantly better compared with placebo ($p=0.043$) while the 4.5 g/night dose was not ($p=0.063$). These results combined with results from the secondary endpoints discussed below, were viewed as establishing a minimally effective (4.5 g/night) and effective (6 g/night) dose for study in Phase 3.

In the Phase 2 study, the secondary efficacy endpoints with a significant overall treatment effect showed a consistent trend of greater response with the 6 g/night dose. Results of the secondary endpoints analyzed by LOCF included statistically significant reductions from baseline to endpoint (Week 8) for severity of daytime sleepiness (ESS) and sleep impairment (JS), and significantly less difficulty from being sleepy or tired while performing specific activities (FOSQ) for subjects in both sodium oxybate groups compared to placebo (Table 8). Improvement in pain measured by change in mean pain VAS score was statistically significant for the 6 g/night dose with the 4.5 g/night dose approaching significance. Improvement in pain measured by the percentage of responders (ie, subjects who achieved $\geq 30\%$ reduction in pain VAS from baseline) was statistically significant for both doses. Improvements in patient global assessment approached significance, and improvement in physical function (SF-36 PCS) was not statistically significant. Results for secondary efficacy endpoints with a significant overall treatment effect are presented in Table 8.

Table 8. Summary of Secondary Efficacy Endpoints with Significant Overall Treatment Effect: Change from Baseline to Endpoint and Responder Analysis (Week 8) (ITT Population, LOCF)

Efficacy Measure	Sodium Oxybate			Overall P value
	Placebo (n=66)	4.5 g/night (n=62)	6 g/night (n=67)	
Pain VAS				
Change, LS Mean (SE)	-9.82 (2.624)	-17.24 (2.754)	-20.01 (2.626)	0.018
Comparison to placebo P value ^a		0.051	0.006	
Responder ^b n (%)	15 (23.8)	24 (41.4)	30 (47.6)	0.017 ^c
Comparison to placebo P value ^c		0.039	0.005	
Fatigue VAS				
Change, LS Mean (SE)	-11.28 (2.645)	-19.29 (2.776)	-20.74 (2.647)	0.011 ^d
Comparison to placebo P value ^d		0.038	0.004	
FIQ Total Score				
Change, LS Mean (SE)	-13.15 (2.621)	-21.02 (2.763)	-20.05 (2.589)	0.040 ^d
Comparison to placebo P value ^d		0.028	0.029	
Epworth Sleepiness Scale				
Change, LS Mean (SE)	-1.0 (0.67)	-3.1 (0.71)	-3.7 (0.66)	0.007 ^d
Comparison to placebo P value ^d		0.011	0.004	
Jenkins Sleep Scale				
Change, LS Mean (SE)	-3.6 (0.74)	-6.8 (0.78)	-6.8 (0.72)	0.003 ^d
Comparison to placebo P value ^d		0.003	0.002	
FOSQ Total Score				
Change, LS Mean (SE)	0.88 (0.474)	2.54 (0.496)	2.23 (0.465)	0.005 ^d
Comparison to placebo P value ^d		0.003	0.008	

^a Pairwise comparisons were obtained using t-tests from the ANOVA model.

^b Responders were subjects who achieved $\geq 30\%$ reduction in pain VAS from baseline.

^c Analysis results are based on chi-square tests.

^d Overall P values and P value for pairwise comparisons are based on ANOVA on ranked data.

Note: With the exception of the responder analysis, analysis results are based on ANOVA, with treatment and center as the factors and 0.05 as the significance level. Interaction of center by treatment is included if it is significant ($p < 0.10$).

Sources: OMC-SXB-26 CSR Tables 15.2.2.1.2, 15.2.2.1.3, 15.2.10.1.2, 15.2.3.1.2, 15.2.8.2, 15.2.9.2, 15.2.11.1.2

The Phase 2 study used nocturnal PSG as an objective pharmacodynamic endpoint for sleep measures. Sleep is commonly disrupted in fibromyalgia patients, and the relationship between disturbed sleep and pain in fibromyalgia has been well documented. The mechanism of action of sodium oxybate in fibromyalgia may be in part due to its profound effects on sleep. Additionally, PSG data provided a way to integrate the narcolepsy experience with sodium oxybate into dose selection decisions for the fibromyalgia population, as the pattern of sleep disturbances in patients with fibromyalgia is similar to that seen in patients with narcolepsy (e.g., increased arousals and waking from sleep, decreased NREM sleep including decreased slow-wave sleep). Consolidation of sleep in narcolepsy patients is linked to efficacy.

Key findings of the PSG assessments are summarized in [Table 9](#). The 6 g/night dose showed profound, statistically significant pharmacodynamic effects that were generally not observed with the 4.5 g/night dose.

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Table 9. Summary of Objective Measures of Sleep: Change from Baseline to Endpoint (Week 8) (ITT Population, Observed Data)

Efficacy Measure	Placebo (n=66)	Sodium oxybate ^a		Overall P value ^b
		4.5 g/night (n=62)	6 g/night (n=67)	
Total Sleep Time (minutes)				
Change, LS Mean (SE)	12.3 (10.19)	-11.4 (11.17)	40.0 (11.73)	0.006
Sleep Efficiency (%)				
Change, LS Mean (SE)	3.4 (2.08)	-2.1 (2.28)	9.0 (2.40)	0.003
Sleep Onset Latency (minutes)				
Change, LS Mean (SE)	-0.3 (5.30)	4.4 (5.73)	-5.8 (6.03)	0.461
Wake After Sleep Onset (minutes)				
Change, LS Mean (SE)	-16.6 (7.52)	3.1 (8.24)	-39.9 (8.66)*	0.002
REM Sleep (minutes)				
Change, LS Mean (SE)	-2.8 (4.88)	-26.5 (5.35)†	-20.8 (5.62)*	0.003
NREM (minutes)				
Change, LS Mean (SE)	14.3 (9.09)	21.5 (11.10)	60.9 (11.13)†	0.005
Stage 1 Sleep (minutes)				
Change, LS Mean (SE)	-2.1 (3.42)	-3.2 (3.74)	-7.8 (3.93)	0.516
Stage 2 Sleep (minutes)				
Change, LS Mean (SE)	15.2 (8.82)	15.5 (10.78)	52.1 (10.80)†	0.018
Stage 3/4 Sleep (minutes)				
Change, LS Mean (SE)	-2.5 (6.17)	12.2 (6.76)	19.5 (7.11)*	0.049

^a Pair-wise comparisons of sodium oxybate with placebo were obtained using t-tests from the ANOVA model; ‡=p<0.001; †=p<0.01; *=p<0.05

^b Analysis results are based on ANOVA with treatment and center as the factors and 0.05 as the significance level. Interaction of center by treatment is included if it is significant (p<0.1).

Sources: OMC-SXB-26 CSR Tables 15.2.17.2, 15.2.16.2, 15.2.20.2, 15.2.15.2, 15.2.18.2, 15.2.19.2, 15.2.22.1.2, 15.2.23.1.2, 15.2.24.1.2

SAFETY

Sodium oxybate was generally safe and well tolerated by subjects with fibromyalgia in this study. No deaths were reported by the investigators. See [Section 4.4](#) for a detailed discussion of safety in the Phase 2 and 3 studies.

4.3.1.5 Rationale for Phase 3 Studies

Two small exploratory clinical studies of sodium oxybate conducted by Scharf and colleagues (1998a and 2003) in patients with fibromyalgia provided initial support for the 4.5 and 6 g doses. The results of the Phase 2 study (OMC-SXB-26) indicated the benefit of the 4.5 and 6 g doses and suggested that 4.5 g was the minimal effective dose. Both doses were selected for study in the Phase 3 program. The choice of 4.5 g/night as the lowest dose to study in Phase 3 is consistent not only with the Phase 2 efficacy and PSG results, but also with the pharmacology of the drug (see [Section 2.2](#)), as it had previously been estimated that single doses of at least 2 to 3 g (roughly equivalent to the individual divided doses recommended in the treatment of fibromyalgia) are required for sodium oxybate to act as an agonist at GABA_B receptors. Initial plans to also study a 9 g dose were dropped after consultation with FDA, and the two large Phase 3 trials (06-008 and 06-009) on the effects of 4.5 and 6 g sodium oxybate in fibromyalgia were conducted. The duration of treatment in the

Phase 3 controlled studies was 14 weeks based on input from the FDA and was designed to provide an adequate duration to assess safety and efficacy.

4.3.2 Summary of the Phase 3 Controlled Studies (06-008 and 06-009)

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SAFETY AND EFFICACY STUDIES OF SODIUM OXYBATE IN SUBJECTS WITH FIBROMYALGIA

4.3.2.1 Study Design: Phase 3 Controlled Studies (06-008 and 06-009)

Two Phase 3 randomized, double-blind, placebo-controlled studies were conducted: 06-008 was conducted at sites in the US and 06-009 was conducted at sites in the US and in Europe. The Phase 3 controlled studies were designed to test the hypothesis that therapeutic doses of sodium oxybate (4.5 and 6 g/night administered in two equally divided doses) would improve the pain, fatigue, sleep disturbance, and impaired functioning from fibromyalgia in a meaningful proportion of subjects after 14 weeks of treatment.

The primary inclusion criteria were that subjects must have been 18 years of age or older, met the American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia, and had average baseline scores $\geq 50/100$ mm on the pain VAS. The primary exclusion criteria were that subjects must not have had current Major Depressive Disorder, Generalized Anxiety Disorder, any history of substance abuse, other painful conditions, or BMI ≥ 40 kg/m². Subjects were also excluded if they were receiving disability benefits for chronic pain or were unwilling to discontinue other medications for fibromyalgia or alcohol. Subjects with moderate or severe sleep apnea who were treated with continuous positive airway pressure (CPAP) were allowed to participate. Subjects with BMI ≥ 35 to <40 kg/m² were eligible to participate only after a polysomnogram indicated a nighttime Apnea-Hypopnea Index (AHI) <15 and oxygen saturation $>80\%$. Detailed inclusion and exclusion criteria are provided in [Appendix B](#).

Subjects who met screening criteria entered a withdrawal/washout phase in which they were withdrawn from all prohibited medications. At the end of the washout period, subjects entered a 1-week baseline period to allow documentation of baseline fibromyalgia symptoms. Subjects who continued to meet all enrollment criteria entered the 14-week, double-blind treatment period. Subjects were randomized in a 1:1:1 ratio to receive sodium oxybate 4.5 g/night, sodium oxybate 6 g/night, or placebo in two equally divided doses each night. Sodium oxybate was initiated at 4.5 g/night for all subjects randomized to active treatment. For subjects randomized to the 6 g/night group, sodium oxybate was maintained at 4.5 g/night for the first 2 weeks then increased to 6 g/night. Subjects then received their fixed randomized dose for 12 weeks; subsequent changes in dose were not allowed, and subjects unable to tolerate the established dose were discontinued from the trial. The use of rescue medication (acetaminophen) was allowed throughout the trial and was documented.

The Phase 3 controlled studies evaluated the effect of sodium oxybate on various fibromyalgia symptoms, such as pain, functionality, fatigue, changes in overall fibromyalgia condition (subject and physician assessments), and sleep disturbance. Efficacy assessments were evaluated at appropriate time points throughout the trials. Subjects used electronic diaries to record pain and fatigue VAS assessments three times a day and to record rescue medication use once a day in the morning. Efficacy assessments and timing of the assessments are described in [Appendix C](#).

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In the prespecified plans for analysis, the primary endpoint was pain severity response (defined as the proportion of subjects in each treatment group who had at least a 30% reduction in overall pain VAS from baseline to Week 14). Consensus recommendations of IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) characterize 30% and 50% reductions in pain as reflecting moderate and substantial improvements, respectively (Dworkin et al. 2008). The primary analysis method was the BOCF method. In addition, the LOCF method was used. As a post-hoc sensitivity analysis, a mixed model repeated measures (MMRM) analysis was also performed on key efficacy endpoints.

Five sequential secondary efficacy parameters were planned:

1. Functionality Response: The proportion of subjects who had at least a 30% reduction in Fibromyalgia Impact Questionnaire (FIQ) total score from baseline to endpoint.
2. Fatigue: The mean change from baseline to endpoint in fatigue VAS.
3. PGI-c Response: The proportion of subjects who had a response of “very much better” or “much better” at endpoint.
4. SF-36 Physical Component: The mean change from baseline to endpoint in SF-36 Physical Component Summary (PCS) score, a health-related quality of life (HRQoL) measure.
5. Sleep Patterns: The mean change from baseline to endpoint in Jenkins Scale (JS).

All tests were two-sided with a significance level of 0.05. The first null hypothesis to be tested was that there was no difference among the three treatment groups in the primary efficacy parameter, Pain Severity Response. This hypothesis was tested at the 0.05 significance level. Provided an overall treatment difference was found in favor of sodium oxybate treatment groups, then secondary efficacy parameter 1 (Functionality Response) was tested. If an overall treatment difference was found, then secondary efficacy parameter 2 (Fatigue) was tested. This procedure continued down the list of primary and then secondary parameters until a non-significant ($p \geq 0.05$) overall p-value was reached.

For parameters exhibiting an overall treatment difference in favor of sodium oxybate treatment groups, pairwise comparisons between sodium oxybate 4.5 g/night and placebo, and between sodium oxybate 6 g/night and placebo were conducted at the 0.05 significance level to identify effective doses.

For the purposes of this document, the primary, sequential secondary, and other key secondary endpoints (ie, Functional Outcomes of Sleep Questionnaire [FOSQ], Manual Tender Point Survey [MTPS], and Fibromyalgia Syndrome Composite) are presented.

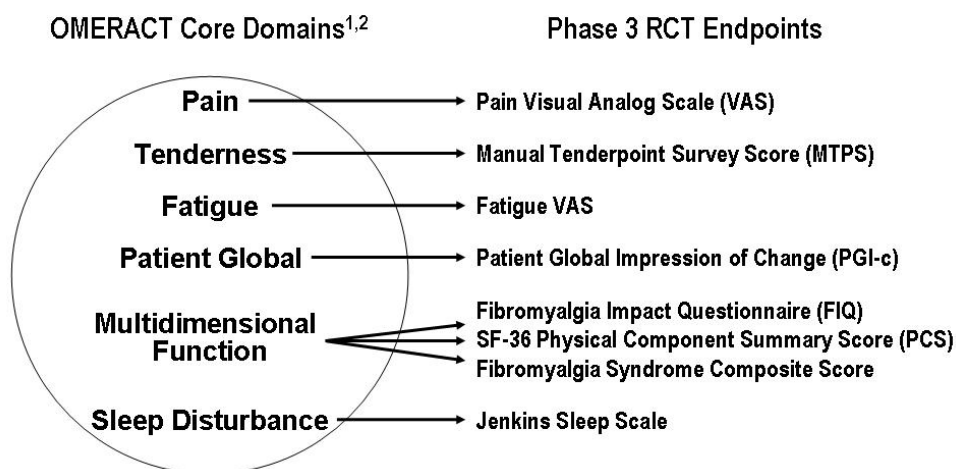
Safety was assessed throughout the studies by the incidence of study adverse events (AEs) and changes in physical examination findings, electrocardiograms (ECG), clinical laboratory tests, vital sign measurements. Changes in the Beck Depression Inventory-II (BDI-II) and Mini International Neuropsychiatric Interview (MINI) Major Depressive Episode and Suicidality modules were used throughout the trials to assess depression and suicidality.

ENDPOINTS FOR EFFICACY EVALUATION

The multiple endpoints studied in the Phase 2 and 3 trials were highly relevant to fibromyalgia patients, who experience a constellation of debilitating symptoms. The endpoints chosen fulfill the OMERACT 9 Fibromyalgia Workshop recommendations to study multiple core domains, including pain, tenderness, fatigue, patient global, multidimensional function, and sleep disturbance in all fibromyalgia treatment clinical trials (Mease et al. 2007, 2009b). These domains were identified in an iterative process with physicians and patient partners in Delphi exercises (Mease et al. 2009b) (Figure 4).

Figure 4 OMERACT Core Fibromyalgia Symptom Domains

Phase 3 Study Endpoints Match OMERACT Core Fibromyalgia Symptom Domains



¹ Choy, EH et al. Rheum Dis Clin N Am 35 (2009) 329–337

² Mease P, et al. J Rheumatol 2007; 34: 1415-1425.

OMERACT = Outcome Measures in Rheumatoid Arthritis Clinical Trials (now Outcome Measures in Rheumatology)

Validated instruments exist to measure these domains; the instruments used include pain VAS, Fibromyalgia Impact Questionnaire (FIQ), fatigue VAS, PGI-c, SF-36 Quality of Life Questionnaire, Jenkins Sleep Scale (JS), FOSQ, and MTPS. Descriptions of these endpoints are included in [Appendix C](#).

4.3.2.2 Disposition: Phase 3 Controlled Studies (06-008 and 06-009)

In Study 06-008, 547 subjects were treated, and 334 subjects (60.9% of randomized subjects) completed the study. While the rate of discontinuations for any reason was similar among the three treatment groups, discontinuation rates due to adverse events were higher in the sodium oxybate groups than in the placebo group, and the discontinuation rate due to lack of efficacy was higher in the placebo group than in the sodium oxybate groups. Overall, 80.5% of subjects who completed 06-008 continued into the Phase 3, open-label study (06-010). Subject disposition is summarized in [Table 10](#).

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Table 10. Summary of Subject Disposition, ITT Population, Study 06-008

	Placebo n (%)	Sodium Oxybate		Total n (%)
		4.5 g/night n (%)	6 g/night n (%)	
No. Subjects Randomized	183	182	183	548
No. Subjects Treated	183 (100.0)	182 (100.0)	182 (99.5)	547 (99.8)
No. Subjects Completed	111 (60.7)	119 (65.4)	104 (56.8)	334 (60.9)
No. Subjects Discontinued	72 (39.3)	63 (34.6)	79 (43.2)	214 (39.1)
Adverse event(s)	20 (10.9)	35 (19.2)	42 (23.0)	97 (17.7)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal of consent	11 (6.0)	10 (5.5)	15 (8.2)	36 (6.6)
Lost to follow up	6 (3.3)	3 (1.6)	5 (2.7)	14 (2.6)
Lack of study drug efficacy	30 (16.4)	12 (6.6)	13 (7.1)	55 (10.0)
Sponsor decision	2 (1.1)	1 (0.5)	2 (1.1)	5 (0.9)
Investigator decision	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)
Protocol deviation/violation	2 (1.1)	1 (0.5)	1 (0.5)	4 (0.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Entered long-term, open-label trial (06-010) ^a	86 (77.5)	101 (84.9)	82 (78.8)	269 (80.5)

Note: Primary reasons for discontinuation are listed. Percentages are based on number of subjects randomized.

^a Data from the interim analysis database for the four-month safety update.

Source: Post-text Table 15.1.1.2 in the 06-008 CSR

In Study 06-009, 571 subjects were treated, and 376 subjects (65.6% of randomized subjects) completed the study. Rates of discontinuation due to adverse events were higher in the sodium oxybate treatment groups compared with the placebo group. Overall, 77.7% of subjects who completed 06-009 continued into the Phase 3, open-label study (06-010). Subject disposition is summarized in Table 11.

Table 11. Summary of Subject Disposition, ITT Population, Study 06-009

	Placebo n (%)	Sodium Oxybate		Total n (%)
		4.5 g/night n (%)	6 g/night n (%)	
No. Subjects Randomized	188	195	190	573
No. Subjects Treated	188 (100.0)	194 (99.5)	189 (99.5)	571 (99.7)
No. Subjects Completed	131 (69.7)	129 (66.2)	116 (61.1)	376 (65.6)
No. Subjects Discontinued	57 (30.3)	66 (33.8)	74 (38.9)	197 (34.4)
Adverse event(s)	11 (5.9)	30 (15.4)	40 (21.1)	81 (14.1)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawal of consent	6 (3.2)	8 (4.1)	5 (2.6)	19 (3.3)
Lost to follow up	5 (2.7)	4 (2.1)	4 (2.1)	13 (2.3)
Lack of study drug efficacy	23 (12.2)	18 (9.2)	19 (10.0)	60 (10.5)
Sponsor decision	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)

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Table 11. Summary of Subject Disposition, ITT Population, Study 06-009

	Placebo n (%)	Sodium Oxybate		Total n (%)
		4.5 g/night n (%)	6 g/night n (%)	
Investigator decision	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.3)
Protocol deviation/violation	9 (4.8)	4 (2.1)	4 (2.1)	17 (3.0)
Other	1 (0.5)	1 (0.5)	2 (1.1)	4 (0.7)
Entered long-term, open-label trial (06-010) ^a	101 (77.1)	98 (76.0)	93 (80.2)	292 (77.7)

Note: Primary reasons for discontinuation are listed. Percentages are based on number of subjects randomized.

^a Data from the interim analysis database for the four-month safety update.

Source: Post-text Table 15.1.1.2 in the 06-009 CSR

4.3.2.3 Demographics and Baseline Characteristics: Phase 3 Controlled Studies (06-008 and 06-009)

Overall, the population studied in these trials was representative of the adult fibromyalgia population in terms of demographics, fibromyalgia symptomatology, disease characteristics, and prior medication use. In addition, the participants in the sodium oxybate studies were demographically very similar to those in 17 published clinical trials with medications now approved in the US for fibromyalgia ([Hauser et al. 2010](#)). Baseline symptoms of pain and poor function were similarly high for the sodium oxybate-studied population and the population in 10 published clinical studies with other medications ([Arnold et al. 2004, 2005, 2008](#); [Clauw et al. 2008](#); [Crofford et al. 2005, 2008](#); [Gendreau et al. 2005](#); [Mease et al. 2008, 2009a](#); [Russell et al. 2008](#)).

Of subjects in the Phase 3 placebo-controlled studies, 750 were randomized to sodium oxybate (377 subjects to sodium oxybate 4.5 g/night and 373 subjects to sodium oxybate 6 g/night) and 371 subjects were randomized to placebo. Overall, demographic characteristics were similar between the All Sodium Oxybate group and the placebo group (Table 12). The study populations were primarily female, Caucasian, and overweight, with a mean age of 47 years. On average, subjects had experienced fibromyalgia symptoms for 10 years and had a time since first fibromyalgia diagnosis of approximately 5 years. At baseline, mean scores for the investigator rated Clinical Global Impression of Severity (CGI-s), which is rated on a scale of 1 to 7 with higher scores indicating more severe illness, indicated that most subjects were moderately or markedly ill ([Table 13](#)).

Table 12. Summary of Demographic and Baseline Characteristics, Phase 3 Placebo-Controlled Studies

Characteristic	Placebo (N=371)	Sodium Oxybate 4.5 g/night (N=377)	Sodium Oxybate 6 g/night (N=373)	All Sodium Oxybate (N=750)
Age (y)				
Mean (SD)	46.7 (10.59)	46.8 (11.24)	47.0 (11.14)	46.9 (11.18)
Age Category (y), n (%)				
18–64	360 (97.0)	361 (95.8)	355 (95.2)	716 (95.5)
≥65	11 (3.0)	16 (4.2)	18 (4.8)	34 (4.5)

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Table 12. Summary of Demographic and Baseline Characteristics, Phase 3 Placebo-Controlled Studies

Characteristic	Placebo (N=371)	Sodium Oxybate 4.5 g/night (N=377)	Sodium Oxybate 6 g/night (N=373)	All Sodium Oxybate (N=750)
Sex, n (%)				
Female	335 (90.3)	341 (90.5)	337 (90.3)	678 (90.4)
Ethnicity, n (%)				
Hispanic or Latino	50 (13.5)	35 (9.3)	36 (9.7)	71 (9.5)
Not Hispanic or Latino	321 (86.5)	342 (90.7)	337 (90.3)	679 (90.5)
Race, n (%)				
White	340 (91.6)	346 (91.8)	336 (90.1)	682 (90.9)
Weight (kg)				
N	369	377	372	749
Mean (SD)	76.3 (15.22)	75.5 (14.79)	77.1 (14.82)	76.3 (14.82)
Body Mass Index (kg/m²)				
N	369	377	372	749
Mean (SD)	28.1 (4.96)	27.7 (4.45)	28.2 (4.73)	28.0 (4.60)
Median	27.7	27.6	28.2	28.0
Minimum, maximum	15.4, 42.6	16.4, 38.8	17.2, 41.5	16.4, 41.5
Body Mass Index Category (kg/m²), n (%)				
N	369	377	372	749
<30	232 (62.9)	258 (68.4)	231 (62.1)	489 (65.3)
≥30	137 (37.1)	119 (31.6)	141 (37.9)	260 (34.7)

Note: This table includes data from Studies 06-008 and 06-009.

Table 13. Summary of Fibromyalgia History, Phase 3 Placebo-Controlled Studies

Characteristic	Placebo (N=371)	Sodium Oxybate 4.5 g/night (N=377)	Sodium Oxybate 6 g/night (N=373)	All Sodium Oxybate (N=750)
Time since first fibromyalgia symptoms (y)				
N	364	371	365	736
Mean (SD)	9.2 (7.62)	10.1 (9.18)	9.8 (8.96)	9.9 (9.07)
Time since first fibromyalgia diagnosis (y)				
N	371	377	373	750
Mean (SD)	5.2 (6.13)	5.7 (6.47)	5.2 (6.03)	5.5 (6.26)
Clinical Global Impression of Severity At Baseline				
N	371	377	372	749
Mean (SD)	4.3 (1.07)	4.4 (0.97)	4.3 (1.00)	4.4 (0.99)

Note: This table includes data from Studies 06-008 and 06-009.

At baseline, subjects reported high levels of pain, fatigue, significant difficulty in daily functioning, and mean SF-36 PCS scores approximately two standard deviations worse than the US normal population, indicating poor physical functioning on this HRQoL measure. The following mean baseline scores were observed in the Phase 3 controlled studies:

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- Pain by the pain VAS, 71 to 73 on a scale of 0 to 100, in which higher scores indicate worse pain
- Fatigue by the fatigue VAS, 71 to 75 on a scale of 0 to 100, in which higher scores indicate worse fatigue
- Functionality by FIQ total score, 62 to 64 on a scale of 0 to 100, in which higher scores indicate worse functionality
- Sleep impairment by JS total score, 15 to 16 on a scale of 0 to 20, in which higher scores indicate greater sleep impairment
- SF-36 PCS score, 29 to 31 on a scale of 0 to 100, with higher scores indicating better functioning. Each SF-36 norm-based summary score and subscale had a mean score of 50 and a standard deviation (SD) of 10 for the general US population in 1998.
- FOSQ total score, 13 to 14 on a scale from 5 to 20, with lower scores indicating greater difficulty in everyday functioning due to feeling “sleepy” or “tired”

Subjects entering the Phase 3 trials had significant sleep disturbance based on self-reports at baseline, with a majority of subjects who reported poor or fair sleep for a duration of ≥ 5 years, sleep duration of ≤ 6 hours/night, ≥ 3 awakenings per night, and time awake during the night ≥ 0.5 hours. Subjects at baseline also had significant tenderness and stiffness as measured by the Tender Point Index and the FIQ stiffness subscale, respectively.

According to fibromyalgia history collected at baseline, about two-thirds of subjects in the Phase 3 studies had used non-pharmacologic therapy and more than 95% used pharmacologic therapy to treat their symptoms. In the Phase 3 controlled studies, subjects were to maintain any non-pharmacologic nutritional and/or exercise regimens and/or behavioral, massage, physical, or cognitive therapies that they had been on for the last 3 months.

The most common previous medications used by subjects in the Phase 3 controlled studies included other scheduled medications including opiates, benzodiazepines, and sedative hypnotics. Table 14 lists previous fibromyalgia treatments in order of the most common in either controlled trial.

Table 14 **Fibromyalgia Treatment History, Phase 3 Placebo-Controlled Studies, ITT Population**

	Study 06-008	Study 06-009
No. of Subjects	548	573
Received Previous Treatment for Fibromyalgia, n (%)	536 (97.8)	558 (97.4)
Received Previous Nonpharmacological Treatment, n (%)	361 (65.9)	398 (69.5)
Received Previous Pharmacologic Treatments, n (%)	530 (96.7)	549 (95.8)
Acetaminophen (paracetamol)	448 (81.8)	396 (69.1)
Nonsteroidal anti-inflammatory	416 (75.9)	410 (71.6)
Skeletal muscle relaxant	253 (46.2)	253 (44.2)
Opiate	191 (34.9)	208 (36.3)
Aspirin	192 (35.0)	133 (23.2)
SSRI	150 (27.4)	156 (27.2)

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Table 14 **Fibromyalgia Treatment History, Phase 3 Placebo-Controlled Studies, ITT Population**

	Study 06-008	Study 06-009
Sedative/hypnotic	145 (26.5)	106 (18.5)
Benzodiazepine	73 (13.3)	126 (22.0)
SNRI	47 (8.6)	106 (18.5)
Tricyclic antidepressant	61 (11.1)	94 (16.4)
Pregabalin ^a	61 (11.1)	93 (16.2)
Steroid	77 (14.1)	75 (13.1)
Anticonvulsant	40 (7.3)	79 (13.8)
Tender point injection	55 (10.0)	60 (10.5)
Guaifenesin	50 (9.1)	13 (2.3)
Monoamine oxidase inhibitor	4 (0.7)	18 (3.1)
Dopamine agonist	5 (0.9)	9 (1.6)
Lithium	3 (0.5)	1 (0.2)
Other	23 (4.2)	59 (10.3)
GHB/sodium oxybate/Xyrem	0	0

GHB=gamma hydroxybutyrate, SNRI=serotonin/norepinephrine reuptake inhibitor, SSRI=selective serotonin reuptake inhibitor

^aPregabalin is listed separately from other anticonvulsants because data were collected for it specifically on the CRF

Note: Percentages are based on nonmissing data. A subject may be included in more than one category of previous treatment for fibromyalgia; therefore, counts and percentages for each drug listed may not add up to the total count and percentage.

Source: Post-text Tables 15.1.6 in 06-008 and 15.1.6 in 06-009

Overall, patients in the controlled studies with sodium oxybate were demographically and symptomatically comparable to previously studied fibromyalgia patients, both in the literature on approved treatments and in the fibromyalgia literature overall ([Wolfe et al. 1997a, 1997b, 2010; Bennett et al. 2007](#)).

4.3.2.4 Phase 3 Controlled Study Results (06-008 and 06-009)

EFFICACY

Efficacy results across the Phase 3 controlled studies are presented in [Table 15](#) for the primary endpoint, sequential secondary endpoints specified in the analysis plans for the Phase 3 controlled studies, and other key secondary endpoints. Overall, both doses of sodium oxybate provided statistically significant and clinically meaningful benefits across all endpoints, including in pain, function, fatigue, and sleep disturbance. Sodium oxybate 6 g/night did not provide numerically superior results compared with sodium oxybate 4.5 g/night in the BOCF analyses. However, a subgroup analysis demonstrated the utility of the higher dose and will be discussed in [Section 4.3.8](#).

Table 15. Efficacy Results Across the Phase 3 Controlled Studies (06-008, 06-009) (ITT Populations, BOCF Analysis): Primary, Sequential Secondary, and Other Key Secondary Endpoints of the Phase 3 Controlled Studies

Endpoint/Symptom Domain	06-008				06-009			
	Placebo (N=183)	SXB 4.5 g/night (N=182)	SXB 6 g/night (N=183)	Overall p-value	Placebo (N=188)	SXB 4.5 g/night (N=195)	SXB 6 g/night (N=190)	Overall P-value
PRIMARY ENDPOINT								
Pain VAS/Pain								
Responder (≥30% reduction), n (%)	50 (27.3)	84 (46.2)	72 (39.3)	<0.001	38 (20.2)	69 (35.4)	67 (35.3)	0.001
95% CI for response rate	(20.9, 33.8)	(38.9, 53.4)	(32.3, 46.4)		(14.5, 26.0)	(28.7, 42.1)	(28.5, 42.1)	
p-value vs. placebo	N/A	<0.001	0.015		N/A	<0.001	0.001	
95% CI difference from placebo (%)	N/A	(9.1, 28.5)	(2.4, 21.6)		N/A	(6.3, 24.0)	(6.2, 23.9)	
SEQUENTIALLY ANALYZED SECONDARY ENDPOINTS								
FIQ Total Score/Function								
Responder (≥30% reduction), n (%)	55 (30.1)	84 (46.2)	72 (39.3)	0.007	41 (21.8)	77 (39.5)	76 (40.0)	<0.001
95% CI for response rate	(23.4, 36.7)	(38.9, 53.4)	(32.3, 46.4)		(15.9, 27.7)	(32.6, 46.3)	(33.0, 47.0)	
p-value vs. placebo	N/A	0.002	0.062		N/A	<0.001	<0.001	
95% CI difference from placebo (%)	N/A	(6.3, 25.9)	(-0.4, 19.0)		N/A	(8.6, 26.7)	(9.1, 27.3)	
Fatigue VAS/Fatigue								
Change from baseline, LS Mean (SE)	-15.07 (2.053)	-24.01 (2.010)	-20.96 (2.011)	0.006	-11.86 (1.927)	-20.18 (1.934)	-19.26 (1.899)	0.004
p-value vs. placebo	N/A	0.002	0.035		N/A	0.002	0.007	
95% CI difference from placebo	N/A	(-14.45, -3.43)	(-11.36, -0.42)		N/A	(-13.68, -2.95)	(-12.71, -2.08)	
PGI-c/Overall Improvement								
Responder (very much or much better), n (%)	41 (22.4)	73 (40.1)	61 (33.3)	0.001	26 (13.8)	51 (26.2)	57 (30.0)	<0.001
95% CI for response rate	(16.4, 28.4)	(33.0, 47.2)	(26.5, 40.2)		(8.9, 18.8)	(20.0, 32.3)	(23.5, 36.5)	
p-value vs. placebo	N/A	<0.001	0.020		N/A	0.003	<0.001	
95% CI difference from placebo (%)	N/A	(8.4, 27.0)	(1.8, 20.0)		N/A	(4.4, 20.2)	(8.0, 24.3)	
SF-36 PCS/Function								
Change from baseline, LS Mean (SE)	3.48 (0.611)	6.01 (0.599)	5.95 (0.599)	0.003	2.58 (0.569)	4.93 (0.564)	4.83 (0.563)	0.004
p-value vs. placebo	N/A	0.003	0.003		N/A	0.003	0.005	
95% CI difference from placebo	N/A	(0.89, 4.17)	(0.85, 4.11)		N/A	(0.82, 3.88)	(0.69, 3.79)	
JS Total Score/Sleep								
Change from baseline, LS Mean (SE)	-2.5 (0.43)	-4.7 (0.42)	-4.5 (0.42)	<0.001	-2.1 (0.36)	-3.4 (0.36)	-4.2 (0.36)	<0.001
p-value vs. placebo	N/A	<0.001	<0.001		N/A	0.007	<0.001	
95% CI difference from placebo	N/A	(-3.4, -1.1)	(-3.1, -0.8)		N/A	(-2.3, -0.4)	(-3.1, -1.1)	

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Table 15. Efficacy Results Across the Phase 3 Controlled Studies (06-008, 06-009) (ITT Populations, BOCF Analysis): Primary, Sequential Secondary, and Other Key Secondary Endpoints of the Phase 3 Controlled Studies

Endpoint/Symptom Domain	06-008				06-009			
	Placebo (N=183)	SXB 4.5 g/night (N=182)	SXB 6 g/night (N=183)	Overall p-value	Placebo (N=188)	SXB 4.5 g/night (N=195)	SXB 6 g/night (N=190)	Overall P-value
OTHER SECONDARY ENDPOINTS								
FOSQ Total Score/Sleep								
Change from baseline, LS Mean (SE)	1.21 (0.235)	2.00 (0.230)	1.81 (0.230)	0.038	0.70 (0.214)	1.71 (0.212)	1.54 (0.212)	0.001
p-value vs. placebo	N/A	0.015	0.060		N/A	<0.001	0.005	
95% CI difference from placebo	N/A	(0.16, 1.42)	(-0.03, 1.23)		N/A	(0.43, 1.58)	(0.25, 1.42)	
MTPS Site Scores/Tenderness								
Change from baseline, LS Mean (SE)	-19.62 (2.814)	-30.91 (2.756)	-27.65 (2.757)	0.011	-10.20 (2.300)	-20.85 (2.282)	-17.06 (2.276)	0.003
p-value vs. placebo	N/A	0.003	0.036		N/A	<0.001	0.032	
95% CI difference from placebo	N/A	(-18.85, -3.73)	(-15.53, -0.53)		N/A	(-16.84, -4.46)	(-13.13, -0.58)	
Fibromyalgia Syndrome Composite								
(≥30% reduction in pain VAS, ≥30% reduction in FIQ total score, very much or much better in PGI-c), n (%)	30 (16.4)	56 (30.8)	56 (30.6)	0.002	20 (10.6)	40 (20.5)	44 (23.2)	0.004
95% CI for response rate	(11.0, 21.8)	(24.1, 37.5)	(23.9, 37.3)		(6.2, 15.0)	(14.8, 26.2)	(17.2, 29.2)	
p-value vs. placebo	N/A	0.001	0.001		N/A	0.008	0.001	
95% CI difference from placebo (%)	N/A	(5.8, 23.0)	(5.6, 22.8)		N/A	(2.7, 17.1)	(5.1, 20.0)	

BOCF=baseline observation carried forward, CI=confidence interval, FIQ=Fibromyalgia Impact Questionnaire, FOSQ=Functional Outcomes of Sleep Questionnaire, ITT=intent-to-treat, JS=Jenkins Sleep Scale, LS=least squares, MTPS=Manual Tender Point Survey, N/A=not applicable, PCS=Physical Component Summary, PGI-c=Patient Global Impression of Change, SE=standard error, SF-36=Short Form-36, SXB=sodium oxybate, VAS=visual analog scale
Note: The endpoint for Studies 06-008 and 06-009 was Week 14.

Source: ISE, 06-008 final report Table 15.2.10.1.2, and 06-009 final report Table 15.2.10.1.2

Primary Variable: Responder Analysis of Pain VAS (Phase 3 controlled studies)

When using the primary efficacy endpoint of ≥30% reduction in pain from baseline to endpoint (BOCF, ITT population), sodium oxybate demonstrated a statistically significant overall treatment effect in the two Phase 3 placebo-controlled studies (Table 15). The higher responder rates for both sodium oxybate treatments (4.5 and 6 g/night) were statistically significant compared with placebo in both Studies 06-008 and 06-009. The results from various analyses on pain (discussed below) indicate a statistically significant improvement in pain, with clinically meaningful moderate and substantial pain reductions. Statistically significant reductions in pain were seen as early as one week and were maintained over 14 weeks.

In 06-008, BOCF pain VAS reductions at Week 14 of at least 50%, reflecting substantial pain reduction, were observed for 39.6% and 30.1% of subjects in the sodium oxybate 4.5

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and 6 g/night groups, respectively, compared with 18.6% in the placebo group ($p < 0.001$ and $p = 0.011$ for the pairwise comparisons of sodium oxybate 4.5 and 6 g/night with placebo, respectively).

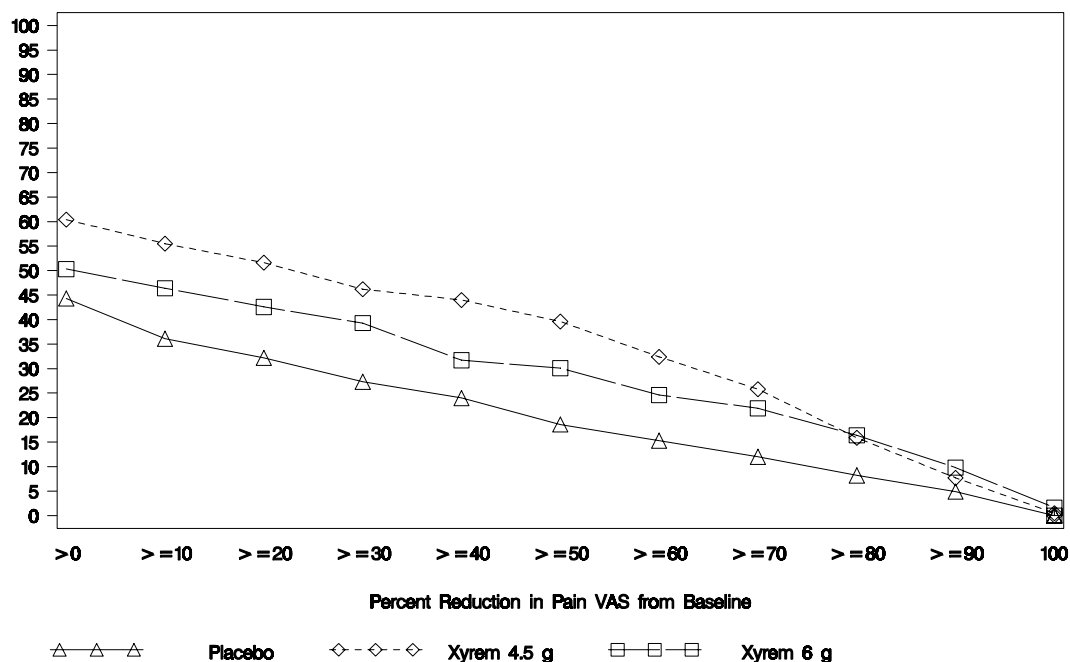
In 06-009, BOCF pain VAS reductions at Week 14 of at least 50% were observed for 24.1% and 26.8% of subjects in the sodium oxybate 4.5 and 6 g/night groups, respectively, compared with 11.7% in the placebo group ($p = 0.002$ and $p < 0.001$ for the pairwise comparisons of sodium oxybate 4.5 and 6 g/night with placebo, respectively).

The magnitude of these effects has substantial clinical relevance for patients with fibromyalgia. Farrar and colleagues (2001) found that a reduction of 2 of 10 points on an 11-point Likert scale or a reduction of 30% corresponded to “much improved” or “very much improved” on the anchor assessment of PGI-c. Further, the consensus recommendations of IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) characterize 30% and 50% reductions in pain as reflecting moderate and substantial improvements, respectively (Dworkin et al. 2008). Therefore, these data demonstrate a robust and consistent effect of sodium oxybate in clinically meaningful reductions in pain in fibromyalgia patients.

The percentages of subjects achieving specified reductions in pain VAS (0% to 100% in 10 percentage point increments) at Week 14 (BOCF) in the two Phase 3 controlled studies are presented in Figure 5 for 06-008 and Figure 6 for 06-009.

In both studies, both sodium oxybate treatments provided a significantly higher proportion of subjects with $\geq 50\%$ pain relief than did placebo. In the BOCF analysis, there were significant overall treatment effects in pain VAS reductions of at least 80% ($p \leq 0.036$) in 06-008 and at least 90% in 06-009 ($p \leq 0.048$). In 06-008, pairwise comparisons of sodium oxybate treatments with placebo were generally statistically significant up through pain VAS reductions of at least 80% ($p \leq 0.044$), with exceptions noted for sodium oxybate 6 g/night versus placebo at two pain reduction cutoff points of greater than 0% and at least 40%. In 06-009, pairwise comparisons of sodium oxybate treatments with placebo were generally statistically significant up through pain VAS reductions of at least 90% ($p \leq 0.039$), with an exception noted for the comparison of sodium oxybate 6 g/night with placebo at pain reductions of greater than or equal to 90%.

Figure 5. Percentage of Subjects Achieving Specified Reductions in Pain VAS at Week 14, Study 06-008, ITT Population, BOCF Analysis

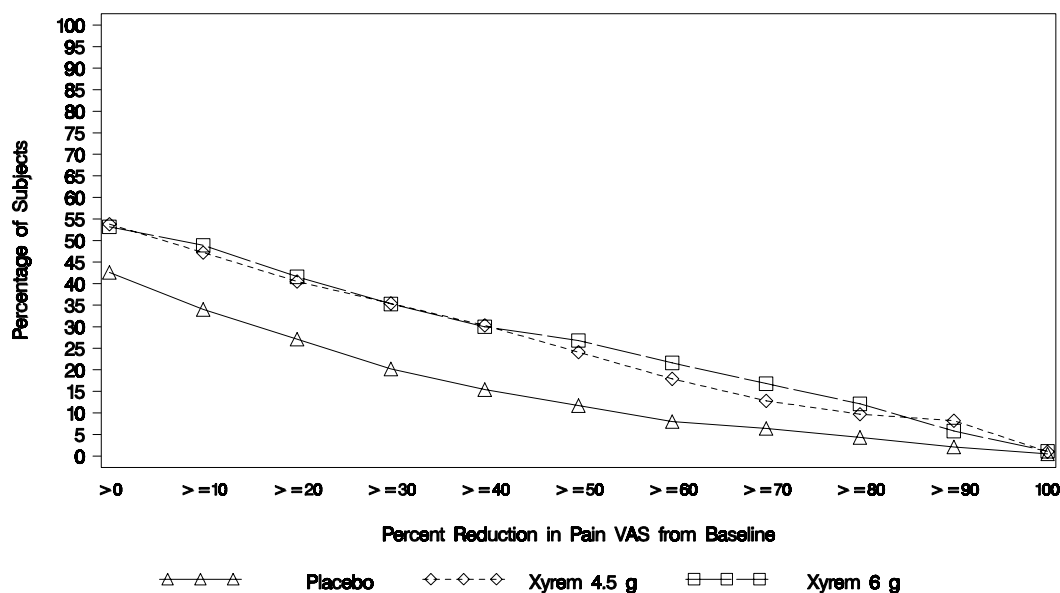


BOCF=baseline observation carried forward, ITT=intent-to-treat, VAS=visual analog scale

Note: Statistical comparisons are provided in the text.

Source: 06-008, CSR Figure 15.1.2.1 and 06-008 CSR, Table 15.2.1.1.3

Figure 6. Percentage of Subjects Achieving Specified Reductions in Pain VAS at Week 14, Study 06-009, ITT Population, BOCF Analysis



BOCF=baseline observation carried forward, ITT=intent-to-treat, VAS=visual analog scale

Note: Statistical comparisons are provided in the text.

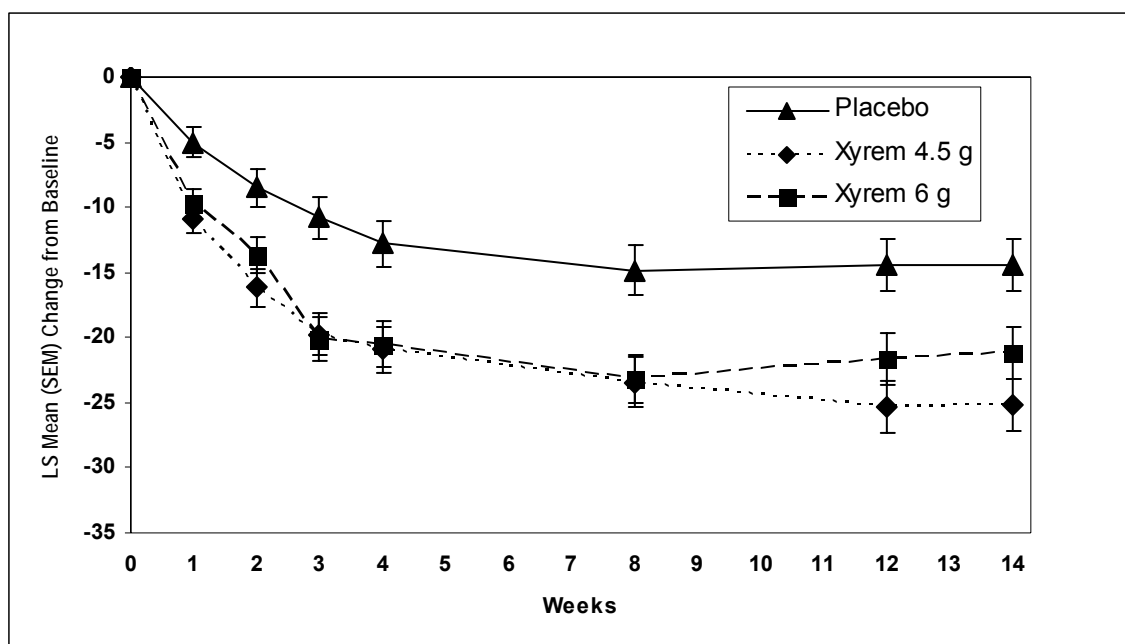
Source: 06-009 CSR, Figure 15.1.2.1 and 06-009 CSR, Table 15.2.1.1.3

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Analysis of Change from Baseline in Pain VAS over Time: Phase 3 Controlled Studies (06-008 and 06-009)

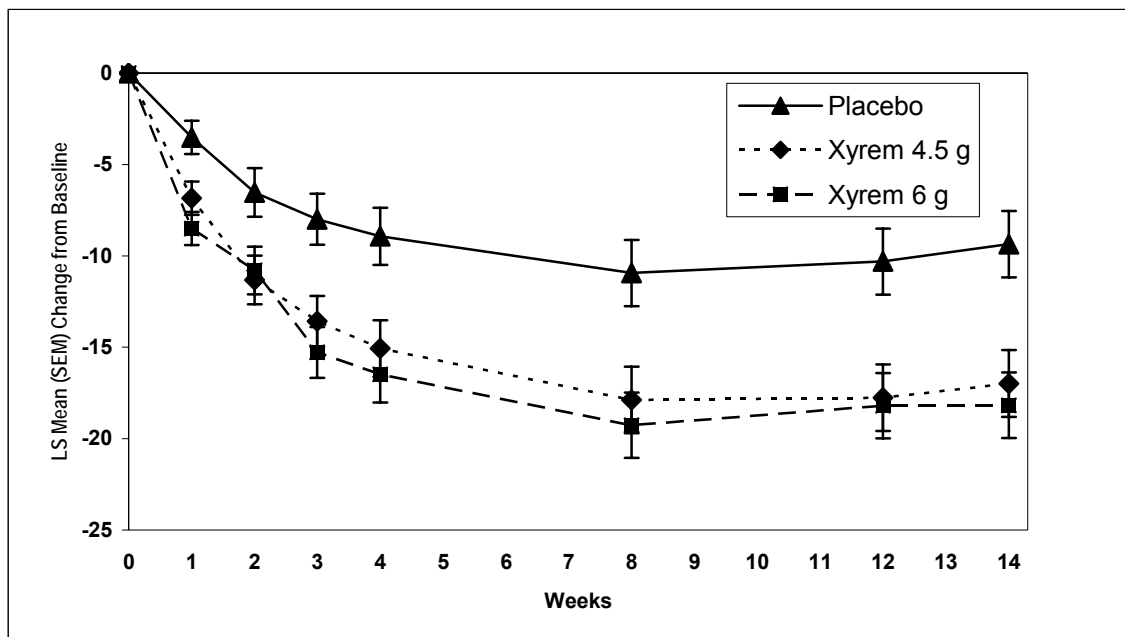
Reductions in pain were seen as early as one week, increased in magnitude over the next several weeks, and were maintained throughout the remainder of the treatment period in both studies. In the BOCF analysis, there was a statistically significant overall treatment effect in pain VAS changes from baseline at all time points in both studies beginning at Week 1 ($p \leq 0.019$ [06-008] and $p \leq 0.020$ [06-009] across all time points). The pairwise comparisons to placebo in LS mean pain VAS for both sodium oxybate treatment groups were statistically significant at all time points ($p \leq 0.043$ [06-008] and $p \leq 0.022$ [06-009]), with the exception in 06-008 of sodium oxybate 6 g/night at Week 13 ($p=0.130$). These reductions were maintained throughout the studies. Figure 7 (06-008) and Figure 8 (06-009) illustrate the separation between the two sodium oxybate treatments and placebo at all time points after treatment initiation.

Figure 7. Change from Baseline in Pain VAS over Time in Study 06-008, ITT Population, BOCF Analysis



BOCF=baseline observation carried forward, ITT=intent-to-treat, LS=least squares, SEM=standard error of the mean, VAS=visual analog scale

Figure 8. Change from Baseline in Pain VAS over Time in Study 06-009, ITT Population, BOCF Analysis



BOCF=baseline observation carried forward, ITT=intent-to-treat, LS=least squares, SEM=standard error of the mean, VAS=visual analog scale

EFFICACY BY SECONDARY VARIABLES

Sodium oxybate treatment has robust and clinically relevant effects on the secondary endpoints, which included FIQ total score, fatigue VAS, PGI-c, SF-36 PCS, JS, FOSQ, MTPS, and Fibromyalgia Syndrome Composite. These well-established, widely utilized measures are highly relevant to fibromyalgia patients, who experience a constellation of debilitating symptoms in addition to pain.

Functionality Response (FIQ)

There was a statistically significant overall treatment effect in functioning with sodium oxybate across both Phase 3 controlled studies for a $\geq 30\%$ reduction in FIQ from baseline to endpoint (BOCF, ITT population), $p = 0.007$ in 06-008, and $p < 0.001$ in 06-009 (Table 15). Responder rates for sodium oxybate versus placebo were 46.2% and 39.3% versus 30.1% in 06-008, and 39.5% and 40.0% versus 21.8% in 06-009. This improvement exceeds the minimum clinically important difference of 14% reduction in FIQ score from baseline defined by Bennett and colleagues (2009) and demonstrates a robust and consistent effect on improving functionality as well as pain in fibromyalgia patients.

Fatigue (Fatigue VAS)

Both Phase 3 controlled studies demonstrated statistically significant and clinically meaningful overall reductions from baseline to endpoint (LS mean, BOCF, ITT) on the fatigue VAS with sodium oxybate treatment: $p = 0.006$ in 06-008 and $p = 0.004$ in 06-009 (Table 15). As with pain, effects were seen as early as one week after treatment initiation and were maintained through the 14 weeks of treatment. In the Phase 3 controlled studies, both

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doses of sodium oxybate were associated with a significant reduction in fatigue compared with placebo.

Sleep Disturbance and Related Functioning (JS, FOSQ)

Sodium oxybate substantially reduced sleep disturbance and reduced difficulty in functioning due to being sleepy or tired.

Subjective assessments of sleep showed a statistically significant and clinically meaningful overall treatment effect with sodium oxybate across both Phase 3 controlled studies in improving sleep impairment (LS mean change from baseline to endpoint using JS, BOCF, ITT) and less difficulty from being sleepy or tired while performing specific activities (LS mean change from baseline to endpoint using FOSQ, BOCF, ITT) ([Table 15](#)).

SF-36 Physical Component Summary

Sodium oxybate significantly improved physical aspects of function in fibromyalgia patients. In addition to its effects on functionality as measured by the FIQ, sodium oxybate showed a statistically significant and clinically meaningful overall treatment effect in increased physical functioning using SF-36 PCS (BOCF, ITT) in the Phase 3 controlled studies. Recent reports in the literature reference a 6-point improvement or a ≥ 2 –5 point improvement on the SF-36 PCS as the minimal clinically important difference (MCID) ([Mease et al. 2009a](#)). In both Phase 3 controlled studies, improvements in LS mean SF-36 PCS scores ranged from 4.83 (6 g/night in 06-009) to 6.01 (4.5 g/night in Study 06-008) ([Table 15](#)), suggesting clinically meaningful improvement in physical functioning.

Overall Improvement (PGI-c)

Patient self-ratings indicate significant improvement with sodium oxybate treatment, with a statistically significant overall treatment effect in the proportion of subjects who felt their symptoms were “much better” or “very much better” (BOCF, ITT) in the Phase 3 controlled studies ([Table 15](#)). The effect was seen at the earliest time point measured (one month after treatment initiation) and continued throughout the duration of the studies. The PGI-c scores of “a little better”, “much better”, and “very much better” are used as anchor measures to determine minimum and greater clinically important improvements in other measures ([Farrar 2001](#), [Dworkin 2008](#)).

Manual Tender Point Survey (MTPS) Scores

In the MTPS, each of the 18 possible tender points was rated by the subject on a 10 point scale in which 0 indicated no pain and 10 indicated the worst pain the subject ever experienced, giving a maximum possible score of 180. Both Phase 3 controlled studies demonstrated statistically significant overall reductions in tenderness from baseline to endpoint (LS mean, BOCF, ITT) on the MTPS with sodium oxybate treatment ($p \leq 0.011$) ([Table 15](#)). Greater reductions in MTPS scores for both the 4.5 and 6 g/night sodium oxybate groups were statistically significant compared with placebo ([Table 15](#)). Reductions in MTPS indicate a reduction in tenderness, an important symptom identified by patients with fibromyalgia ([Mease et al. 2009b](#)).

Composite Endpoint

Fibromyalgia Syndrome Composite: Improvements on composite endpoints indicate a broader impact of treatment than that seen with individual symptom endpoints. There was statistically significant and clinically relevant overall treatment effect with sodium oxybate across the Phase 3 controlled studies on this composite endpoint, which included PGI-c response of “very much better” or “much better,” a $\geq 30\%$ reduction on pain VAS, and a $\geq 30\%$ reduction in FIQ total score from baseline to endpoint (Week 14) using BOCF in the ITT population (Table 15). The significant overall treatment effects of sodium oxybate on this triple composite endpoint comprising pain, function, and patient global assessment demonstrates the robust effects of this compound across multiple symptoms of fibromyalgia.

SAFETY

Sodium oxybate was generally well tolerated in these subjects with fibromyalgia. The safety profile for sodium oxybate treatments in these studies is generally consistent with data from previous clinical trials and postmarketing experience with sodium oxybate. See Section 4.4 for a detailed discussion of safety in the Phase 2 and 3 studies.

4.3.2.5 Efficacy in Subpopulations: Phase 3 Controlled Studies (06-008 and 06-009)

The Phase 3 controlled study results from the responder analysis of pain VAS and FIQ total score were compared in the following subpopulations (Table 16): age, gender, race, baseline disease severity based on the CGI-s, received non-pharmacological treatment versus not, and time since first symptoms of fibromyalgia (< 5 years versus ≥ 5 years). No differences were observed between subgroups with sample sizes large enough to allow meaningful conclusions.

In the subgroups of age (< 65 years), gender (female), and race (Caucasian), sodium oxybate showed statistically significant overall treatment effects in pain VAS and FIQ total score from baseline to endpoint (Table 16). However, these subgroups represent the majority of the overall subject population in these studies; observing the same effect in these large subgroups as in the overall population is expected. The corresponding small subgroups age (≥ 65 years), gender (male), and race (non Caucasian) had sample sizes too small to allow meaningful conclusions.

In the subgroups based on disease severity (CGI-s “moderately ill or less severe” versus “markedly ill or more severe”) and time since first symptoms of fibromyalgia (< 5 years or ≥ 5 years), sodium oxybate showed a statistically significant treatment effect in pain VAS and FIQ total score response in both groups for both dichotomous variables (Table 16), indicating that sodium oxybate is effective in reducing pain and improving functionality in fibromyalgia patients regardless of disease severity or duration.

Baseline factors considered important to the primary efficacy outcome were tested using a logistic regression model. These factors included items from the sleep history, previous fibromyalgia treatment, current non-pharmacological therapy, age at baseline, and age at first fibromyalgia symptoms. These models did not identify any subpopulations that were less likely to respond.

Table 16. Efficacy Results in Subpopulations, ITT Populations, BOCF Analysis, Phase 3 Controlled Studies (06-008, 06-009): Pooled Data

06-008, 06-009 Pooled Data, Week 14								
Endpoint/Domain	Placebo	Sodium Oxybate 4.5 g/night	Sodium Oxybate 6 g/night	Overall P-value	Placebo	Sodium Oxybate 4.5 g/night	Sodium Oxybate 6 g/night	Overall P-value
AGE								
Pain VAS								
		<65 years				≥65 years		
N	360	361	355		11	16	18	
Responder (≥30% reduction), n (%)	86 (23.9)	147 (40.7)	134 (37.7)	<0.001	2 (18.2)	6 (37.5)	5 (27.8)	0.548
P-value vs. placebo	N/A	<0.001	<0.001		N/A	0.280	0.558	
Change from baseline, LS Mean (SE)	-11.37 (1.356)	-20.63 (1.353)	-20.26 (1.354)	<0.001	-14.15 (8.364)	-23.52 (5.956)	-11.95 (4.994)	0.409
P-value vs. placebo	N/A	<0.001	<0.001		N/A	0.467	0.844	
FIQ Total Score								
N	360	361	355		11	16	18	
Responder (≥30% reduction), n (%)	94 (26.1)	153 (42.4)	141 (39.7)	<0.001	2 (18.2)	8 (50.0)	7 (38.9)	0.244
P-value vs. placebo	N/A	<0.001	<0.001		N/A	0.093	0.242	
Change from baseline, LS Mean (SE)	-10.52 (1.109)	-17.93 (1.106)	-17.29 (1.107)	<0.001	-15.61 (9.077)	-15.74 (6.463)	-11.56 (5.419)	0.868
P-value vs. placebo	N/A	<0.001	<0.001		N/A	0.992	0.740	
GENDER								
Pain VAS								
		Male				Female		
N	36	36	36		335	341	337	
Responder (≥30% reduction), n (%)	7 (19.4)	9 (25.0)	12 (33.3)	0.400	81 (24.2)	144 (42.2)	127 (37.7)	<0.001
P-value vs. placebo	N/A	0.571	0.181		N/A	<0.001	<0.001	
Change from baseline, LS Mean (SE)	-9.95 (4.796)	-14.39 (4.662)	-10.77 (5.122)	0.805	-11.35 (1.423)	-21.47 (1.409)	-19.93 (1.410)	<0.001
P-value vs. placebo	N/A	0.534	0.912		N/A	<0.001	<0.001	
FIQ Total Score								
N	36	36	36		335	341	337	
Responder (≥30% reduction), n (%)	9 (25.0)	13 (36.1)	13 (36.1)	0.508	87 (26.0)	148 (43.4)	135 (40.1)	<0.001
P-value vs. placebo	N/A	0.306	0.306		N/A	<0.001	<0.001	
Change from baseline, LS Mean (SE)	-7.71 (3.624)	-14.96 (3.523)	-7.19 (3.870)	0.290	-10.60 (1.168)	-18.57 (1.156)	-17.21 (1.157)	<0.001
P-value vs. placebo	N/A	0.181	0.926		N/A	<0.001	<0.001	

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Table 16. Efficacy Results in Subpopulations, ITT Populations, BOCF Analysis, Phase 3 Controlled Studies (06-008, 06-009): Pooled Data

06-008, 06-009 Pooled Data, Week 14								
Endpoint/Domain	Placebo	Sodium Oxybate 4.5 g/night	Sodium Oxybate 6 g/night	Overall P-value	Placebo	Sodium Oxybate 4.5 g/night	Sodium Oxybate 6 g/night	Overall P-value
RACE								
Pain VAS								
		Caucasian				Non-Caucasian		
N	340	346	336		31	31	37	
Responder ($\geq 30\%$ reduction), n (%)	83 (24.4)	136 (39.3)	122 (36.3)	<0.001	5 (16.1)	17 (54.8)	17 (45.9)	0.005
P-value vs. placebo	N/A	<0.001	<0.001		N/A	0.001	0.009	
Change from baseline, LS Mean (SE)	-11.56 (1.404)	-20.33 (1.388)	-19.55 (1.392)	<0.001	-4.31 (6.663)	-30.15 (6.234)	-17.42 (6.382)	0.037
P-value vs. placebo	N/A	<0.001	<0.001		N/A	0.011	0.185	
FIQ Total Score								
N	340	346	336		31	31	37	
Responder ($\geq 30\%$ reduction), n (%)	88 (25.9)	145 (41.9)	131 (39.0)	<0.001	8 (25.8)	16 (51.6)	17 (45.9)	0.093
P-value vs. placebo	N/A	<0.001	<0.001		N/A	0.037	0.086	
Change from baseline, LS Mean (SE)	-10.54 (1.152)	-18.15 (1.139)	-16.75 (1.142)	<0.001	-7.85 (4.929)	-18.33 (4.611)	-15.94 (4.721)	0.321
P-value vs. placebo	N/A	<0.001	<0.001		N/A	0.152	0.267	
DISEASE SEVERITY (CGI-s)								
Pain VAS								
		Moderately Ill/Less Severe				Markedly Ill/More Severe		
N	218	216	219		153	161	153	
Responder ($\geq 30\%$ reduction), n (%)	56 (25.7)	95 (44.0)	80 (36.5)	<0.001	32 (20.9)	58 (36.0)	59 (38.6)	0.002
P-value vs. placebo	N/A	<0.001	0.014		N/A	0.003	<0.001	
Change from baseline, LS Mean (SE)	-12.74 (1.841)	-23.15 (1.821)	-19.07 (1.836)	<0.001	-10.92 (2.356)	-17.53 (2.272)	-23.20 (2.369)	<0.001
P-value vs. placebo	N/A	<0.001	0.008		N/A	0.032	<0.001	
FIQ Total Score								
N	218	216	219		153	161	153	
Responder ($\geq 30\%$ reduction), n (%)	60 (27.5)	100 (46.3)	83 (37.9)	<0.001	36 (23.5)	61 (37.9)	65 (42.5)	0.001
P-value vs. placebo	N/A	<0.001	0.021		N/A	0.006	<0.001	
Change from baseline, LS Mean (SE)	-12.09 (1.467)	-19.33 (1.451)	-15.24 (1.463)	<0.001	-9.53 (1.990)	-16.12 (1.919)	-21.24 (2.001)	<0.001
P-value vs. placebo	N/A	<0.001	0.100		N/A	0.012	<0.001	

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Table 16. Efficacy Results in Subpopulations, ITT Populations, BOCF Analysis, Phase 3 Controlled Studies (06-008, 06-009): Pooled Data

06-008, 06-009 Pooled Data, Week 14								
Endpoint/Domain	Placebo	Sodium Oxybate 4.5 g/night	Sodium Oxybate 6 g/night	Overall P-value	Placebo	Sodium Oxybate 4.5 g/night	Sodium Oxybate 6 g/night	Overall P-value
USED NON-PHARMACOLOGIC TREATMENT AT BASELINE (Y/N)								
Pain VAS								
		Yes				No		
N	135	140	135		236	237	238	
Responder ($\geq 30\%$ reduction), n (%)	30 (22.2)	52 (37.1)	51 (37.8)	0.008	58 (24.6)	101 (42.6)	88 (37.0)	<0.001
P-value vs. placebo	N/A	0.007	0.005		N/A	<0.001	0.003	
Change from baseline, LS Mean (SE)	-10.32 (2.417)	-18.60 (2.459)	-22.19 (2.402)	<0.001	-13.16 (1.782)	-22.42 (1.754)	-19.71 (1.728)	<0.001
P-value vs. placebo	N/A	0.011	<0.001		N/A	<0.001	0.006	
FIQ Total Score								
N	135	140	135		236	237	238	
Responder ($\geq 30\%$ reduction), n (%)	32 (23.7)	59 (42.1)	53 (39.3)	0.003	64 (27.1)	102 (43.0)	95 (39.9)	<0.001
P-value vs. placebo	N/A	0.001	0.006		N/A	<0.001	0.003	
Change from baseline, LS Mean (SE)	-10.36 (2.003)	-16.85 (2.038)	-18.48 (1.990)	0.005	-11.11 (1.450)	-18.95 (1.427)	-16.99 (1.406)	<0.001
P-value vs. placebo	N/A	0.015	0.002		N/A	<0.001	0.003	
TIME SINCE FIRST FIBROMYALGIA SYMPTOMS								
Pain VAS								
		<5 years				≥ 5 years		
N	116	116	123		248	255	242	
Responder ($\geq 30\%$ reduction), n (%)	27 (23.3)	51 (44.0)	47 (38.2)	0.003	59 (23.8)	99 (38.8)	91 (37.6)	<0.001
P-value vs. placebo	N/A	<0.001	0.013		N/A	<0.001	<0.001	
Change from baseline, LS Mean (SE)	-9.21 (2.594)	-20.49 (2.566)	-17.54 (2.505)	0.006	-11.63 (1.717)	-20.98 (1.690)	-20.92 (1.685)	<0.001
P-value vs. placebo	N/A	0.002	0.018		N/A	<0.001	<0.001	
FIQ Total Score								
N	116	116	123		248	255	242	
Responder ($\geq 30\%$ reduction), n (%)	27 (23.3)	49 (42.2)	48 (39.0)	0.005	67 (27.0)	110 (43.1)	99 (40.9)	<0.001
P-value vs. placebo	N/A	0.002	0.009		N/A	<0.001	0.001	
Change from baseline, LS Mean (SE)	-8.43 (2.159)	-17.23 (2.136)	-15.55 (2.085)	0.008	-10.89 (1.390)	-19.30 (1.368)	-17.88 (1.364)	<0.001
P-value vs. placebo	N/A	0.003	0.015		N/A	<0.001	<0.001	

BOCF=Baseline observation carried forward, CGI-s=Clinical Global Impression of Severity, FIQ=Fibromyalgia Impact Questionnaire, ITT=intent-to-treat, LS=least squares, N/A=not applicable, SE=standard error, SXB=sodium oxybate, VAS=visual analog scale

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4.3.3 Effect Size

The importance of treating multiple symptoms associated with fibromyalgia was recognized in a recent article by Hauser and colleagues (2010) in which the effect sizes for relief of five symptoms were compared for the three approved fibromyalgia drugs. We have calculated the effect sizes for sodium oxybate 4.5 g/night and 6 g/night across the same five domains using BOCF and LOCF data from the Phase 3 controlled studies (Table 17). Effect size was estimated for each sodium oxybate dose versus placebo as the difference between the model-adjusted mean change divided by the estimate of standard deviation (root mean square error).

Table 17 Effect Size Based on Sodium Oxybate Phase 3 Controlled Study Data

Outcome title	Number of study arms	No. of patients on active treatment: SXB 4.5 g/night	No. of patients on active treatment: SXB 6 g/night	Effect size: SXB 4.5 g/night	Effect size: SXB 6 g/night	P value for overall effect
BOCF						
01 Pain	3	377	373	-0.38	-0.34	<0.001
02 Fatigue	3	377	373	-0.35	-0.28	<0.001
03 Sleep	3	377	373	-0.35	-0.40	<0.001
04 Depressed mood	3	377	373	-0.14	-0.15	0.076
05 HRQoL	3	377	373	0.32	0.31	<0.001
LOCF						
01 Pain	3	372	354	-0.38	-0.54	<0.001
02 Fatigue	3	372	354	-0.38	-0.48	<0.001
03 Sleep	3	343	346	-0.46	-0.57	<0.001
04 Depressed mood	3	369	360	-0.07	-0.11	0.3385
05 HRQoL	3	331	328	0.34	0.40	<0.001

Note: HRQoL is represented by the SF-36 Physical Component Summary (SF-36 PCS). SXB=sodium oxybate

The effect sizes for sodium oxybate based on BOCF and LOCF analyses demonstrate a consistent response across all domains with the exception of depressed mood (Table 17). The analysis of the approved fibromyalgia drugs by Hauser and colleagues (2010) demonstrated, for any of the approved drugs, less uniformity of treatment effect among the various domains than is seen in a similar analysis of sodium oxybate data. The uniformity of effect sizes across the domains of pain, fatigue, sleep, and health-related quality of life with sodium oxybate further supports the benefit of sodium oxybate on multiple fibromyalgia symptoms.

4.3.4 Clinical Meaningful Effects based on Minimal Clinically Important Differences (MCID) and “Moderate” Improvements

The clinical significance of the effects of sodium oxybate across core domains in fibromyalgia is derived by comparing the percentage of subjects in the active and placebo groups who reported improvements exceeding the MCID as well as “moderate” improvements (eg, $\geq 30\%$ for pain reduction as endorsed by the IMMPACT group). Typically, LOCF data are used in evaluating MCID, but both LOCF and BOCF data relative to MCID are presented in this section.

Pain: The MCID for VAS scales is well recognized as 10 on a scale of 100 mm. The Pain VAS responder criteria of 30% and 50% pain relief were identified as “moderate” and “substantial” levels of pain relief, respectively, by IMMPACT (Dworkin 2008). Both doses of sodium oxybate were statistically superior to placebo in both Phase 3 controlled studies using these criteria indicating that “moderate” and “substantial” levels of pain relief were achieved in BOCF and LOCF analyses. A significant number of patients achieved relief levels greater than 50%. These responses are clinically meaningful, by definition, but are also important to patients because their pain is unremitting and in most cases, quite long-standing.

Multidimensional Function: The MCID for the FIQ was determined by Bennett (2009) to be a 14% reduction in FIQ score. The 30% responder criteria used for the FIQ response in the Phase 3 controlled studies exceeded this by more than a factor of 2. The 4.5 g/night dose of sodium oxybate, in both studies, and the 6 g/night dose, in the 06-009 study, were statistically superior to placebo using this criteria by BOCF analysis (Table 15) and both doses met this criteria in both studies using LOCF analysis (Table 23 and Table 24), indicating a substantial clinical significance.

Reductions of 30% in the total FIQ score could have impact on poor functioning across many domains including work disability. The odds ratio for being disabled by fibromyalgia increases as FIQ scores increase; patients with FIQ scores from 50-74 (on a 0-100 scale) have been shown to have work disability rates as high as 35% and those with scores above 75 have work disability rates as high as 83% with odds ratios for work disability of 5.43 (95% CI 1.75-16.79) and 35.00 (95% CI 8.70-140.87), respectively (White 1999). Given this description of the potential severity of the condition, it is not surprising that a 14% decrease in FIQ score has been shown to be the MCID in improvement on this measure (Bennett 2009).

The SF-36 PCS score is a combined measure of the physical domains of health-related quality of life. The MCID for the SF-36 scores has been determined to be between 2.5 and 5.0 across a variety of chronic and rheumatologic conditions (Samsa et al. 1999). Recent reports in the fibromyalgia literature reference a 6-point improvement as exceeding MCID or a ≥ 2 -5 point improvement as MCID (Mease et al. 2009a). In the Phase 3 controlled studies, mean improvements in SF-36 scores of 4.83-6.01 by BOCF (Table 15) and of 6.34-8.82 by LOCF (Table 23 and Table 24) met these MCID criteria.

Fatigue: The MCID for VAS scales is well recognized as 10 on a scale of 100 mm. Fatigue is an important symptom to fibromyalgia patients as evidenced by its placement in the core symptom domains by OMERACT. Three criteria were used to determine MCID for fatigue VAS:

- MCID 1 was calculated as the mean change in fatigue VAS for the subset of subjects in the Phase 3 controlled studies who were on active treatment and reported “a little better” on the PGI-c. Using this method, the MCID for fatigue VAS was calculated to be -27.3 based on BOCF and -25.5 based on LOCF (Table 18).
- MCID 2 was responder criteria in the Phase 3 controlled studies for pain VAS and FIQ total score, and is considered a moderate improvement.
- MCID 3 was calculated as the mean percentage reduction for subjects who were on active treatment and responded “a little better” on the PGI-c. Using this method, the

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MCID for fatigue VAS was calculated to be -38% based on BOCF and -36% based on LOCF (Table 18).

Clinically meaningful reductions in fatigue were seen in a greater proportion of subjects on active versus placebo treatment who met these MCID criteria (Table 18). The overall treatment effect for these differences was highly statistically significant for all three analyses ($p < 0.001$) (Table 18).

Table 18 Proportion of Subjects with Improvement Exceeding MCID

Outcome Title	MCID Criteria	% of Subjects with Improvement ≥MCID				Overall p-value
		MCID	Placebo	SXB 4.5 g	SXB 6 g	
BOCF						
Fatigue	MCID 1	-27.3	20.8	36.1	33.2	<0.001
	MCID 2	-30%	25.9	42.4	39.1	<0.001
	MCID 3	-38%	21.6	38.7	33.5	<0.001
Sleep	MCID 1	-5.6	20.5	35.8	35.1	<0.001
LOCF						
Fatigue	MCID 1	-25.5	26.5	44.1	49.7	<0.001
	MCID 2	-30%	31.8	51.6	56.2	<0.001
	MCID 3	-36%	27.3	47.3	49.7	<0.001
Sleep	MCID 1	-5.2	27.8	49.3	50.3	<0.001

MCID 1 was calculated as the mean change in fatigue VAS, or the mean JS, for the subset of subjects in the Phase 3 controlled studies who were on active treatment and reported “a little better” on the PGI-c.

MCID 2 was responder criteria in the Phase 3 controlled studies for pain VAS and FIQ total score, and is considered a moderate improvement.

MCID 3 was calculated as the mean percentage reduction for subjects who were on active treatment and responded “a little better” on the PGI-c.

Subjective Sleep: Sleep disturbance, which was also identified by patients as important and recognized as a core domain by OMERACT, was measured by the Jenkins Sleep Scale (JS). The MCID for the JS was calculated as the mean JS for the subset of subjects in the Phase 3 controlled studies who were on active treatment and reported “a little better” on the PGI-c.

The percentage of subjects in each treatment group who had JS reductions that met or exceeded the MCID (BOCF and LOCF analyses) are shown in Table 18. A greater proportion of subjects on active treatment met or exceeded the BOCF and LOCF MCID values of -5.6 and -5.2, respectively, compared with those on placebo treatment. The overall treatment effect was highly statistically significant for both the BOCF and LOCF analyses ($p < 0.001$).

Tenderness: No MCID has been established for the MTPS scores.

Fibromyalgia Syndrome Composite: Subjects who met the criteria for response had to have a PGI-c response of “very much better” or “much better,” a $\geq 30\%$ reduction on pain VAS, and a $\geq 30\%$ reduction in FIQ total score. The individual criteria within this triple composite individually represent a response greater than an MCID and therefore, the triple composite indicates a robust response to treatment. There is no doubt that a patient who reports moderate pain relief, twice the level of functional improvement as the defined MCID for the FIQ, and an overall response of “much better” or “very much better” has had a

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clinically meaningful response to treatment. Both doses of sodium oxybate in both studies were superior to placebo in providing this level of response to treatment ([Table 15](#)).

Thus, across multiple symptom domains of importance to clinicians treating patients with fibromyalgia and to patients, sodium oxybate has provided clinically meaningful reductions in symptoms of pain, fatigue, and sleep disturbance and a clinically meaningful improvement in function.

4.3.5 Summary of the Phase 3 Uncontrolled Study (06-010)

A LONG-TERM, OPEN-LABEL SAFETY AND EFFICACY STUDY OF SODIUM OXYBATE IN SUBJECTS WITH FIBROMYALGIA

4.3.5.1 Study Design: Phase 3 Uncontrolled Study

The Phase 3 uncontrolled study, 06-010, was open to subjects who completed either of the Phase 3 placebo-controlled studies (06-008 or 06-009). This open-label study was designed to assess the safety and efficacy of sodium oxybate for up to one year of treatment (including 14 weeks in the previous Phase 3 study) and expanded the dose range evaluated to 9 g/night, with flexible titration of individual subjects to effect and tolerability. Eligible subjects were to have been enrolled within 7 days after completing the previous study. The study included 38 weeks on study treatment.

In 06-010, subjects could be titrated to effect. Subjects initiated sodium oxybate at 4.5 g/night divided into two equal doses and remained on this dosing schedule for at least one week. Dose escalations to effect were permitted at least one week apart in increments of 1.5 g nightly (0.75 g per dose), and doses were not to exceed 9 g nightly (divided into two equal 4.5 g doses). Dose reductions to effect or for safety were also allowed at the investigator's discretion. At each visit, the investigator used safety and efficacy data to determine whether to maintain or to adjust the subject's current sodium oxybate dose within a 4.5 to 9 g/night dose range. Subjects were allowed ibuprofen or naproxen, and/or acetaminophen at over-the-counter (OTC) doses as rescue medication.

Efficacy was evaluated using a majority of the same efficacy measures used in the Phase 3 controlled studies. The single primary efficacy endpoint specified in the analysis plan was the Pain Severity Response from the pain VAS, defined as the proportion of subjects who had at least a 30% reduction in overall pain VAS from the prior study (06-008 or 06-009) baseline to study endpoint. In 06-010, analyses of efficacy parameters by study visit in the all-treated population were performed using the observed data approach. Subject data at study endpoint were also summarized.

Secondary efficacy endpoints included pain severity, functionality response (the proportion of subjects who had at least a 30% reduction in FIQ total score from the prior study baseline to study endpoint), FIQ total score, fatigue VAS, PGI-c, SF-36 PCS, FOSQ total score, and Fibromyalgia Syndrome Composite Response. In this study, the FOSQ was used to determine the impact of sleepiness or tiredness on daytime functioning for specific activities by subject self report. The JS was not evaluated in this study.

Except for exploratory analyses of pain VAS response, FIQ total score response, and adverse events by gender, no formal hypotheses were tested. Efficacy data were summarized using descriptive statistics.

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Safety was assessed by the incidence of study AEs and changes in physical examination findings, ECGs, clinical laboratory tests, and vital sign measurements including weight.

4.3.5.2 Disposition: Phase 3 Uncontrolled Study (06-010)

An interim analysis was presented in the NDA on a total of 245 subjects who were treated and either discontinued prematurely or completed the trial. Of these subjects, 176 had completed Study 06-008 and 69 had completed Study 06-009, and a total of 107 subjects (43.7%) completed Study 06-010 as of the interim analysis cutoff date. As reported in the Integrated Safety Summary in the NDA, a total of 561 (79%) subjects who completed the prior controlled trials enrolled in 06-010 (including one subject who was not treated).

In the interim dataset, the most common reason for discontinuation was adverse event (33.5%), which includes non-treatment-emergent and treatment-emergent adverse events in this study, followed by withdrawal of consent (6.9%), lack of study drug efficacy (6.5%), and lost to follow-up (2.9%). A higher percentage of subjects who received placebo in the controlled study discontinued early due to an adverse event compared to those who received either dose of sodium oxybate in the previous controlled study.

4.3.5.3 Demographics and Baseline Characteristics: Phase 3 Uncontrolled Study (06-010)

For the all-treated population in Study 06-010, which was a subset of subjects who completed one of the two double-blind, placebo-controlled studies (06-008 or 06-009), demographic and baseline data were consistent with the patterns observed in the prior studies, demonstrating that these individuals were a representative subset of the population evaluated in the controlled studies.

4.3.5.4 Phase 3 Uncontrolled Study Interim Results (06-010)

EFFICACY

Consistent with the controlled studies, sodium oxybate relieved several key symptoms of fibromyalgia, including high baseline levels of pain, fatigue, and impairments in daily living and physical functioning. The effects of sodium oxybate on multiple symptoms were maintained over time at levels that were clinically significant.

The proportion of responders at study endpoint (subject's last measurement) on the primary efficacy variable ($\geq 30\%$ reduction in overall pain VAS from prior study baseline to endpoint) was 68.2% for all treated subjects. The proportions of responders at study endpoint (subject's last measurement) on the FIQ total score ($\geq 30\%$ reduction from baseline), PGI-c (score of "very much better" or "much better"), and the fibromyalgia syndrome composite (combining pain VAS, FIQ total score, and PGI-c response) were 67.2%, 55.8%, and 44.8%, respectively, for all treated subjects (Table 19).

Table 19 Responder Analyses at Study Endpoint, All Treated Population, Study 06-010

Responder analysis	n	Proportion of Responders at Study Endpoint
Primary endpoint: ≥30% reduction in Pain VAS	239	68.2%
≥30% reduction in FIQ total score	241	67.2%
PGI-c response of “very much better” or “much better”	240	55.8%
Fibromyalgia syndrome composite (≥30% reduction in Pain VAS, ≥30% reduction in FIQ total score, and PGI-c response of “very much better” or “much better”)	239	44.8%

Source: 06-010 Interim CSR In-text Tables 10, 12, and 15 and Post-text Table 15.2.13.1

Substantial improvements from baseline (in the prior controlled study) to study endpoint were also observed for the mean changes in multiple secondary endpoints as well (Table 20).

Table 20 Mean Change from Baseline (in the prior controlled study) to Endpoint in 06-010, Secondary Endpoints

Efficacy Measure	Time Point			
	Baseline		Change from Baseline to Endpoint	
	N	Mean (SD)	N	Mean (SE)
Pain VAS	245	70.88 (13.321)	239	-35.51 (1.772)
FIQ Total Score	245	61.98 (14.394)	241	-29.75 (1.403)
Fatigue VAS	245	72.58 (14.507)	239	-36.80 (1.769)
SF-36 PCS	238	30.32 (9.018)	230	10.39 (0.615)
FOSQ	239	13.75 (3.681)	234	2.87 (0.229)

Source: 06-010 Interim CSR: In text Table 7; Post-text tables 15.2.1.1.6, 15.2.2.1.5, 15.2.3.1, 15.2.5.1.1, 15.2.10.1.1

SAFETY

The safety data indicate that sodium oxybate, titrated to effect and tolerability over a dose range of 4.5 to 9 g/night with a mean dose throughout the study of approximately 6 g per night, was generally well tolerated over 38 weeks of treatment in these adults with fibromyalgia. The safety profile for sodium oxybate treatments in this study is generally consistent with data from previous clinical trials and postmarketing experience with sodium oxybate. See [Section 4.4](#) for a detailed discussion of safety in the Phase 2 and 3 studies.

4.3.6 Persistence of Efficacy and/or Tolerance of Effects

Sodium oxybate was effective in improving fibromyalgia symptoms in the controlled studies (06-008 and 06-009), and these effects were maintained over the course of the 06-010 open-label study. Interim data for subjects who were randomized to sodium oxybate treatment in the controlled studies and who received sodium oxybate treatment for at least 26 (n=105) or 52 weeks (including controlled study exposure) (n=76) are presented in Table 21 and Table 22. The mean changes from baseline for these endpoints are described over the duration of the controlled and open-label trials at the 12-, 26-, 38- and 52-week time points. However, SF-36 was evaluated at alternative time points and PGI-c does not have a baseline value. The JS was not used in Study 06-010, but functionality with respect to sleepiness and tiredness was evaluated using the FOSQ. Note that the interim analysis included only those subjects who completed the trial by the cutoff date, but did not include data for ongoing subjects.

Data for subjects who were exposed to sodium oxybate for at least 26 weeks showed that the reductions in mean scores for pain VAS, FIQ total score, and fatigue VAS, and the improvements in mean scores for FOSQ and SF-36 PCS and the PGI-c rating were maintained through 26 weeks (18 weeks for SF-36 PCS, the last measurement time point for this measure through 26 weeks) (Table 21).

Table 21. Change from Baseline for Efficacy Measures, Phase 3 Studies (06-008, 06-009, and 06-010): Data for Subjects with at least 26 Weeks (≥6 Months) of Exposure

Time point	Baseline		Change From Baseline			
			12 weeks		26 weeks	
	N	Mean (SD)	N	Mean (SE)	N	Mean (SE)
Pain VAS	105	70.82 (12.603)	105	-36.76 (2.543)	104	-41.24 (2.667)
FIQ Total Score	105	60.96 (13.701)	101	-32.07 (2.081)	103	-34.68 (2.096)
Fatigue VAS	105	71.67 (14.614)	105	-36.21 (2.516)	104	-41.49 (2.659)
PGI-c	NA	NA	105	2.4 (1.07)*	104	2.0 (0.87)*
FOSQ Total Score	102	13.67 (3.696)	98	3.53 (0.310)	100	4.11 (0.333)
Time point	Baseline		14 weeks		18 weeks	
	N	Mean (SD)	N	Mean (SE)	N	Mean (SE)
SF-36 PCS	102	30.20 (9.379)	101	9.60 (0.885)	101	11.38 (0.834)

* Mean (SD) results for the given time point are displayed for the PGI-c.

Note: This table sequentially links data from subjects in Studies 06-008 or 06-009 with data from those continuing into Study 06-010. Subjects who were randomized to sodium oxybate treatment groups in Phase 3 placebo-controlled Studies 06-008 and 06-009 are included.

Note: For pain and fatigue VAS, baseline was the average of all available daily averages during the last week of the baseline period. For each post-baseline week, the average of all available daily averages for that week was used. Pain VAS scale is from 0 (no pain) to 100 (worst imaginable pain). Fatigue VAS scale is from 0 (no fatigue) to 100 (worse imaginable fatigue).

For FIQ total score, baseline was the last value collected during the baseline period. The sum of the normalized subscale scores was used, with 0 indicating no impairment and 100 indicating maximum impairment.

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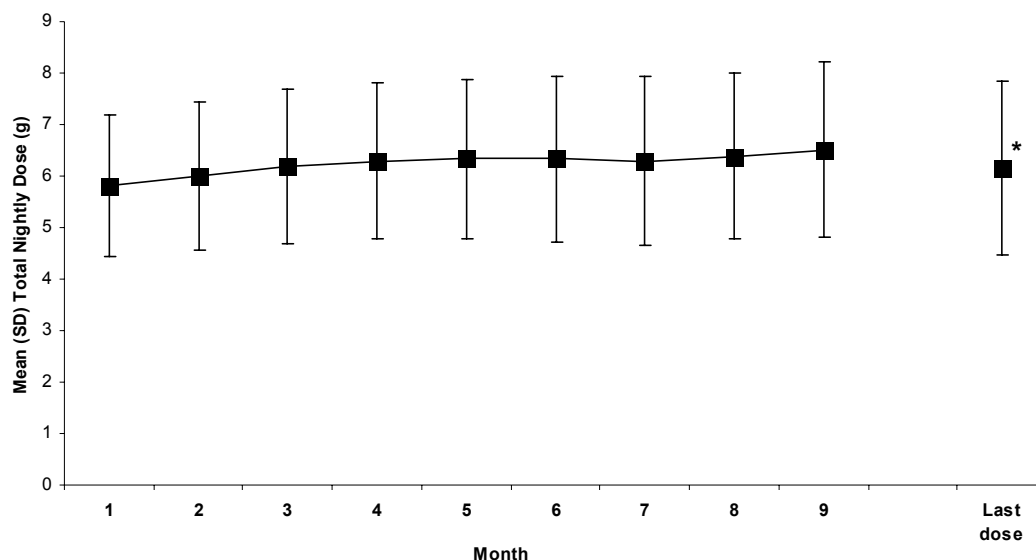
Patient Global Impression of Change is evaluated on a 7-point scale with 1 = Very Much Better, 2 = Much Better, 3 = A Little Better, 4 = No Change, 5 = A Little Worse, 6 = Much Worse, and 7 = Very Much Worse.

FOSQ Total Score is calculated as the mean of all available subscale scores multiplied by 5. The Total Score ranges from 5 to 20, with lower scores indicating more impact from being 'sleepy' or 'tired'.

Higher SF-36 PCS (Physical Component Summary) score indicates better physical health.

The same persistency of effect seen in the 26-week data for pain VAS, FIQ total score, fatigue VAS, PGI-c rating, FOSQ total score, and SF-36 PCS were also seen through 38 and 52 weeks in subjects who received sodium oxybate treatment for 52 weeks (Table 22). No apparent dose tolerance was suggested by the mean dose range seen in the interim data from the 38-week open-label study. Figure 9 displays average dose over time for all doses combined in Study 06-010. As shown in the figure, the mean dose was maintained at approximately 6 g/night throughout the 38-week study.

Figure 9 Mean Total Nightly Dose, All Doses Combined, All-Treated Population in 06-010



* Including subjects who discontinued early.

Source: g_line_mean dose by month_010

Table 22. Change from Baseline for Efficacy Measures, Phase 3 Studies (06-008, 06-009, and 06-010): Data for Subjects with at least 52 Weeks (≥12 Months) of Exposure

Time point	Change From Baseline									
	Baseline		12 weeks		26 weeks		38 weeks		52 weeks	
	N	Mean (SD)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
Pain VAS	76	70.67 (11.922)	76	-41.71 (2.772)	76	-44.23 (3.061)	76	-43.87 (3.169)	75	-43.93 (3.162)
FIQ Total Score	76	60.77 (13.262)	74	-35.86 (2.307)	75	-37.41 (2.470)	76	-37.35 (2.633)	76	-39.56 (2.410)
Fatigue VAS	76	71.82 (13.930)	76	-40.93 (2.853)	76	-44.75 (3.049)	76	-45.49 (3.173)	75	-44.07 (3.242)
PGI-c	NA	NA	76	2.1 (0.79)*	76	1.8 (0.82)*	76	1.9 (0.88)*	76	1.8 (0.85)*
FOSQ Total Score	73	13.70 (3.624)	71	3.77 (0.343)	72	4.10 (0.380)	73	3.81 (0.385)	73	3.94 (0.390)
Time point	Baseline		14 weeks		18 weeks		38 weeks		52 weeks	
	N	Mean (SD)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)	N	Mean (SE)
SF-36 PCS	73	30.04 (9.887)	73	10.86 (0.968)	72	12.49 (0.984)	73	12.11 (1.089)	73	13.25 (1.142)

* Mean (SD) results for the given time point are displayed for the PGI-c.

Note: This table sequentially links data from subjects in Studies 06-008 or 06-009 with data from those continuing into Study 06-010. Subjects who were randomized to sodium oxybate treatment groups in Phase 3 placebo-controlled Studies 06-008 and 06-009 are included.

Note: For pain and fatigue VAS, baseline was the average of all available daily averages during the last week of the baseline period. For each post-baseline week, the average of all available daily averages for that week was used. Pain VAS scale is from 0 (no pain) to 100 (worst imaginable pain). Fatigue VAS scale is from 0 (no fatigue) to 100 (worse imaginable fatigue).

For FIQ total score, baseline was the last value collected during the baseline period. The sum of the normalized subscale scores was used, with 0 indicating no impairment and 100 indicating maximum impairment.

Patient Global Impression of Change is evaluated on a 7-point scale with 1 = Very Much Better, 2 = Much Better, 3 = A Little Better, 4 = No Change, 5 = A Little Worse, 6 = Much Worse, and 7 = Very Much Worse.

FOSQ Total Score is calculated as the mean of all available subscale scores multiplied by 5. The Total Score ranges from 5 to 20, with lower scores indicating more impact from being 'sleepy' or 'tired'.

Higher SF-36 PCS (Physical Component Summary) score indicates better physical health.

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4.3.7 Dosing Recommendations

The recommended doses of sodium oxybate are 4.5 and 6 g/night. The recommended starting dose is 4.5 g/night, divided into two equal doses of 2.25 g each. Based on data from the clinical program in fibromyalgia, the 4.5 g/night dose is expected to provide benefit for a substantial portion of patients. The 6 g/night dose is expected to provide additional benefit for some patients when warranted by individual patient need and tolerability. Analyses supporting these recommendations are discussed below in Section 4.3.8.

4.3.8 Dose Response

There was no pre-planned analysis of dose response included in the analysis plan for these studies, and no statistical comparisons of efficacy between doses were conducted. However, the relative effects of the 4.5 and 6 g doses are seen in the BOCF and LOCF analyses of all efficacy data.

Although the BOCF analyses of most measures did not consistently show a numerically better response for the 6 g dose than for the 4.5 g dose, it should be noted that the BOCF imputation method favors effective lower doses over effective higher doses if the higher doses are associated with more dropouts due to adverse effects. As such, this analysis mixes the safety aspects of the compound into the efficacy results.

In fact, this was the case in both studies: the 6 g group did have a higher rate of dropouts due to adverse events than the 4.5 g group. When analyzed by the LOCF method, which retains the treatment benefits experienced by subjects at the time of discontinuation, both studies show numerically higher levels of response in the 6 g group compared to the 4.5 g group not only for the primary endpoint, but also for most of the sequentially tested secondary endpoints (except the PGI-c in Study 06-008, and the SF-36 PCS and FOSQ Total Score in Study 06-009), and on the composite endpoint ([Table 23](#) and [Table 24](#)).

Table 23. Changes from Baseline to Week 14 in Primary, Sequentially Tested Secondary, and Composite Efficacy Endpoints, ITT Population: Study 06-008 (LOCF Analysis)

Endpoint	Placebo (N=183)	SXB 4.5 g (N=182)	SXB 6 g (N=183)	Overall P-value
Pain VAS				
Responder, n (%)	62 (35.2)	97 (54.2)	100 (58.5)	<0.001
P-value vs. placebo	N/A	<0.001	<0.001	
FIQ Total Score				
Responder, n (%)	69 (38.8)	99 (55.3)	98 (56.0)	0.001
P-value vs. placebo	N/A	0.002	0.001	
Fatigue VAS				
Change from baseline, LS Mean (SE)	-17.57 (2.167)	-27.94 (2.084)	-30.02 (2.144)	<0.001
P-value vs. placebo	N/A	<0.001	<0.001	
PGI-c				
Responder, n (%)	47 (27.2)	84 (48.3)	79 (45.4)	<0.001
P-value vs. placebo	N/A	<0.001	<0.001	
SF-36 PCS				
Change from baseline, LS Mean (SE)	4.96 (0.709)	7.81 (0.684)	8.82 (0.690)	<0.001
P-value vs. placebo	N/A	0.003	<0.001	
JS Total Score				
Change from baseline, LS Mean (SE)	-2.9 (0.48)	-6.1 (0.47)	-6.2 (0.46)	<0.001
P-value vs. placebo	N/A	<0.001	<0.001	
FOSQ Total Score				
Change from baseline, LS Mean (SE)	1.63 (0.289)	2.28 (0.281)	2.32 (0.282)	0.146
P-value vs. placebo	N/A	0.101	0.079	
FM Syndrome Composite^a				
Responder, n (%)	35 (26.1)	59 (40.1)	67 (48.9)	<0.001
P-value vs. placebo	N/A	0.013	<0.001	

FIQ=FM Impact Questionnaire, FM=fibromyalgia, FOSQ=Functional Outcomes of Sleep Questionnaire, ITT=intent-to-treat, JS=Jenkins Sleep Scale, LOCF=last observation carried forward, LS=least squares, N/A=not applicable, PCS=Physical Component Summary, PGI-c=Patient Global Impression of Change, SE=standard error, Synd=syndrome, VAS=visual analog scale

^a Includes pain VAS, FIQ total score, and PGI-c responders

Sources: Post-Text Tables 15.2.1.1.1, 15.2.2.1.1, 15.2.3.1.2, 15.2.4, 15.2.5.1.2, 15.2.6.2, 15.2.11.1.2, and 15.2.14 from study report 06-008

Table 24. Changes from Baseline to Week 14 in Primary, Sequentially Tested Secondary, and Composite Efficacy Endpoints, ITT Population: Study 06-009 (LOCF Analysis)

Endpoint	Placebo	SXB 4.5 g	SXB 6 g	Overall P-value
Pain VAS	N= 183	N=193	N=183	
Responder, n (%)	49 (26.8)	81 (42.0)	94 (51.4)	< 0.001
P-value vs. placebo	N/A	0.002	< 0.001	
FIQ Total Score	N=181	N=190	N=185	
Responder, n (%)	54 (29.8)	95 (50.0)	102 (55.1)	< 0.001
P-value vs. placebo	N/A	< 0.001	< 0.001	
Fatigue VAS	N=183	N=193	N=183	
Change from baseline, LS Mean (SE)	-13.65 (1.939)	-22.96 (1.908)	-26.22 (1.922)	< 0.001
P-value vs. placebo	N/A	< 0.001	< 0.001	
PGI-c	N=181	N=190	N=179	
Responder, n (%)	29 (16.0)	61 (32.1)	71 (39.7)	< 0.001
P-value vs. placebo	N/A	< 0.001	< 0.001	
SF-36 PCS	N=161	N=169	N=168	
Change from baseline, LS Mean (SE)	3.57 (0.683)	6.42 (0.667)	6.34 (0.668)	0.003
P-value vs. placebo	N/A	0.002	0.003	
JS Total Score	N=166	N=176	N=174	
Change from baseline, LS Mean (SE)	-2.9 (0.42)	-4.9 (0.41)	-5.9 (0.41)	< 0.001
P-value vs. placebo	N/A	< 0.001	< 0.001	
FOSQ Total Score	N=163	N=173	N=173	
Change from baseline, LS Mean (SE)	0.98 (0.276)	2.10 (0.268)	2.09 (0.268)	0.003
P-value vs. placebo	N/A	0.003	0.004	
FM Syndrome Composite^a	N=153	N=158	N=156	
Responder, n (%)	21 (13.7)	42 (26.6)	53 (34.0)	< 0.001
P-value vs. placebo	N/A	0.005	< 0.001	

FIQ=FM Impact Questionnaire, FM=fibromyalgia, FOSQ=Functional Outcomes of Sleep Questionnaire, ITT=intent-to-treat, JS=Jenkins Sleep Scale, LOCF=last observation carried forward, LS=least squares, N/A=not applicable, PCS=Physical Component Summary, PGI-c=Patient Global Impression of Change, SE=standard error, Synd=syndrome, VAS=visual analog scale

^a Includes pain VAS, FIQ total score, and PGI-c responders

Sources: Post-Text Tables 15.2.1.1.1, 15.2.2.1.1, 15.2.3.1.2, 15.2.4, 15.2.5.1.2, 15.2.6.2, 15.2.11.1.2, and 15.2.14 from study report 06-009

These findings demonstrate a clear benefit with the 4.5 g dose and indicate an increased benefit with the 6 g dose across multiple symptom domains for some subjects.

EXPLORATORY ANALYSES: CONTROLLED STUDIES 06-008 AND 06-009

Two additional types of analyses were conducted to explore the dose-response relationship for the 4.5 and 6 g doses.

Mixed Model Repeated Measures Analysis (MMRM)

As the magnitude of the dose response appears to differ with imputation method (BOCF vs LOCF), an alternate imputation method (MMRM) was used to examine dose response, as this method has been proposed as being more robust ([Mallinckrodt et al. 2003](#)).

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The MMRM analysis performed on change from baseline for pain VAS and FIQ total score showed numerically greater reductions for the 6 g dose versus the 4.5 g dose in both studies (Table 25).

Table 25. MMRM Analyses on Change from Baseline (Difference from Placebo) for Pain VAS and FIQ Total Score

	Study 06-008		Study 06-009	
	4.5 g	6 g	4.5 g	6 g
Pain VAS, LS Mean Difference from Placebo (SE)	-13.06 (3.22)	-16.85 (3.28)	-10.06 (2.87)	-16.46 (2.90)
FIQ Total Score, LS Mean Difference from Placebo (SE)	-7.88 (2.51)	-10.56 (2.55)	-11.28 (2.24)	-12.34 (2.27)

Source: Post-Text Tables 19.1, 19.2, 20.1, and 20.2 from the ISE

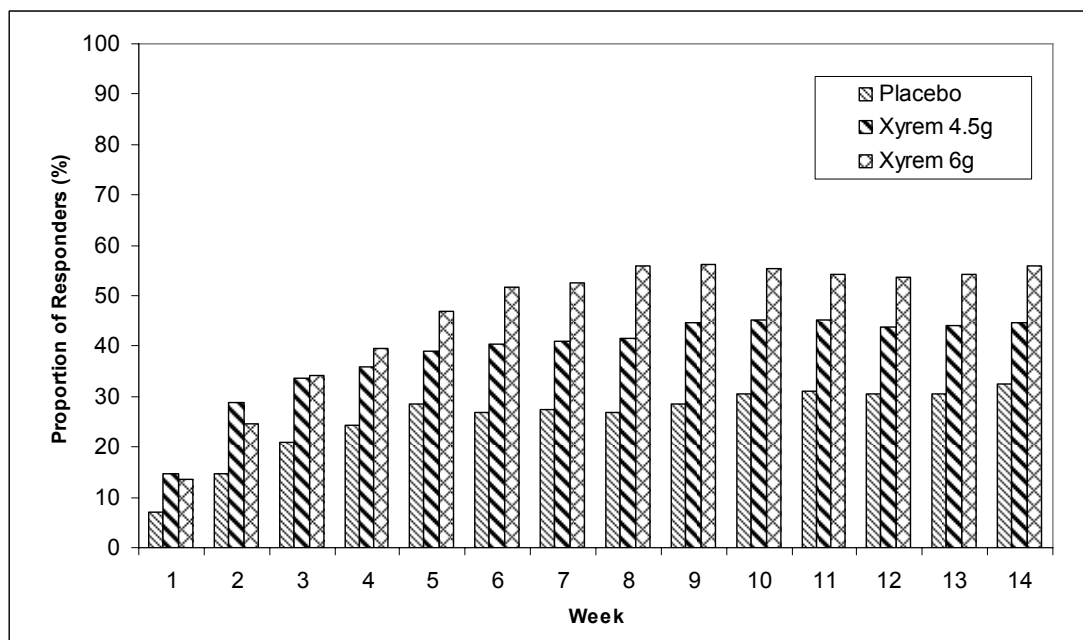
These comparisons versus placebo were all statistically significant (p-values 0.002 to <0.001) and demonstrate increased efficacy with the 6 g dose consistent with a positive dose response.

Analysis of Pain VAS by Baseline Pain

The above analyses showed some increase in efficacy with the 6 g dose. Since it might be expected that those patients suffering from more severe pain at baseline could show more improvement at the higher dose, an additional exploratory analysis was conducted examining pain VAS responses by baseline pain scores for the two Phase 3 controlled studies combined. A cutoff pain VAS of 70 was chosen for this analysis, as Pain VAS ≥ 70 indicates severe pain ([Anderson 2005](#)). These analyses confirmed a greater efficacy response with the higher dose in patients with more severe pain at baseline, which is also consistent with a positive dose response.

Pain VAS Response. The proportions of responders for those subjects with baseline pain VAS ≥ 70 by study week are presented in [Figure 10](#), which illustrates a clear separation in response between the two doses for those subjects with more pronounced pain at baseline. The difference in response between the 4.5 and 6 g dose was statistically significant ($p < 0.05$) at Weeks 6 through 9 and at Week 14. Pain VAS Response at Week 14 is compared for subjects with less and more severe baseline pain in [Table 26](#).

Figure 10. Responder^a Analysis of Pain VAS by Baseline Pain VAS: Phase 3 Placebo-Controlled Studies (Baseline Pain VAS ≥ 70 : LOCF Data)



^aPain VAS responders are those subjects who had $\geq 30\%$ reduction in pain VAS from baseline to endpoint.
Source: g_bar_pain responders over time_baseline pain vas GE 70

Table 26. Change from Baseline in Pain VAS Response at Week 14: Studies 06-008 and 06-009 Pooled (LOCF Data)

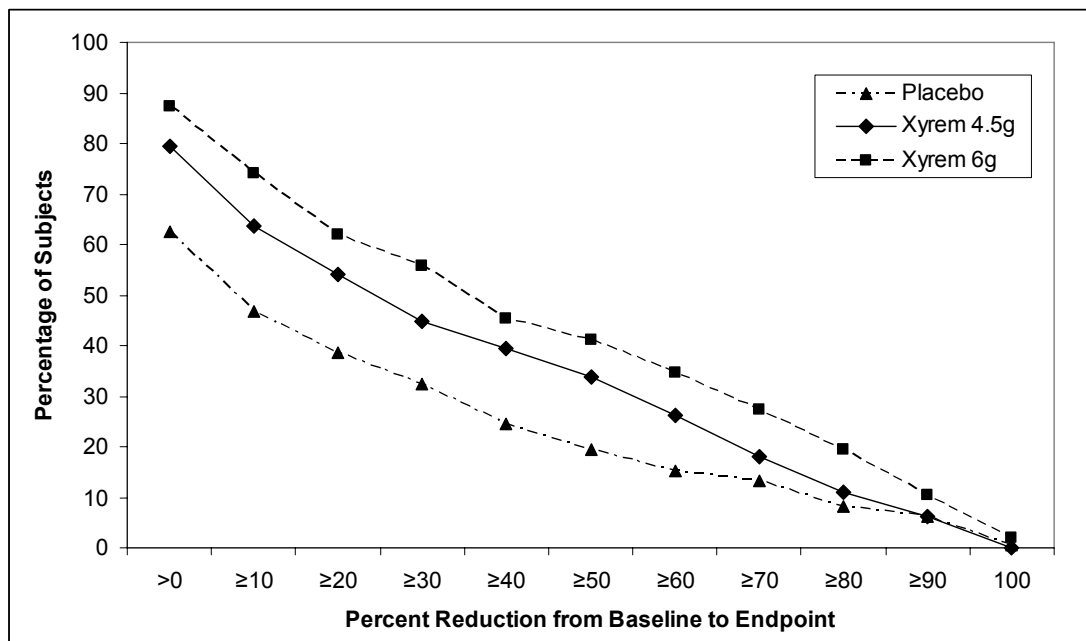
Baseline Pain VAS < 70	Placebo	SXB 4.5 g	SXB 6 g	Overall P-value
Number of subjects	162	182	164	
Responders ($\geq 30\%$ Reduction in Pain VAS)	47 (29.0%)	93 (51.1%)	88 (53.7%)	<0.001
P-value vs placebo		<0.001	<0.001	
Baseline Pain VAS ≥ 70				
Number of subjects	197	190	190	
Responders ($\geq 30\%$ Reduction in Pain VAS)	64 (32.5%)	85 (44.7%)	106 (55.8%)	<0.001
P-value vs placebo		0.013	<0.001	
P-value vs 4.5 g dose			0.031	

Source: Table 2.1.9 of the ISE

These data indicate that while the 4.5 g dose provides clear benefits in pain relief for subjects at different pain levels, for some subjects with higher pain levels at baseline (score 70 or above), the 6 g dose provides additional benefit in reducing pain. Similarly, there is a greater separation in doses when looking at percent of subjects with more severe baseline pain achieving a specified reduction in pain VAS (Figure 11), with the differences between the 4.5 and 6 g doses achieving statistical significance at 0, 10, 30, 70, and 80 percent reduction in pain VAS. Change in mean pain scores from baseline showed a similar benefit for patients with more severe pain at baseline (Figure 12). The increased response with the 6 g dose versus the 4.5 g dose was statistically significant ($p < 0.05$) at Weeks 8 and 14.

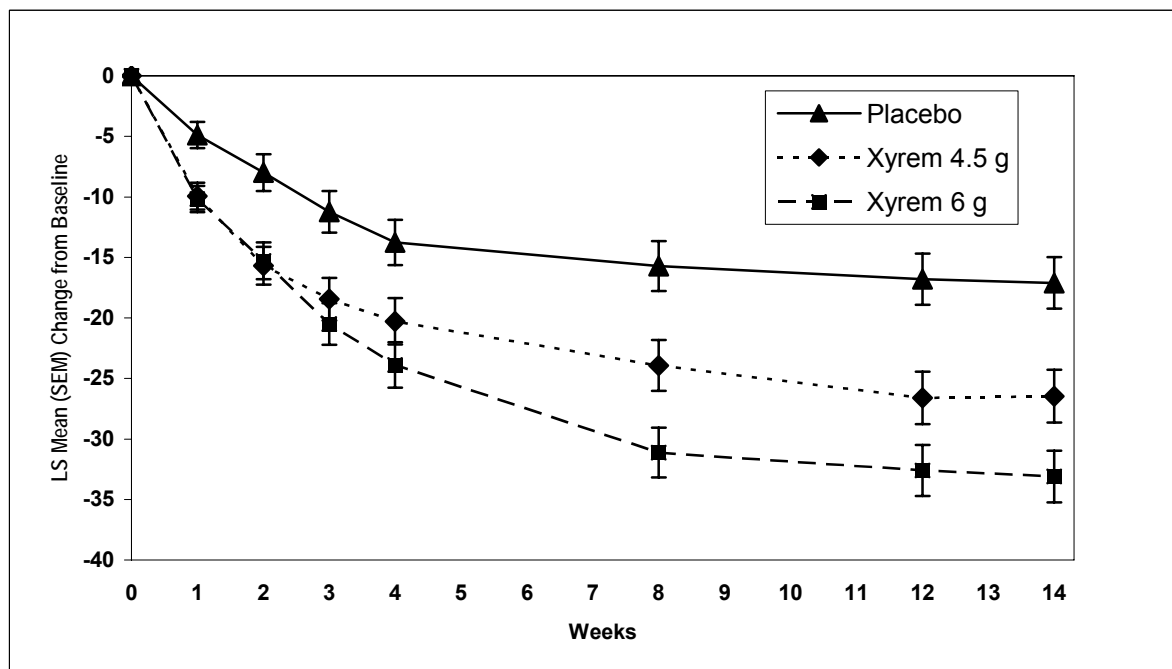
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Figure 11. Percentage of Subjects Achieving Specified Reduction in Pain VAS at Endpoint by Baseline Pain VAS: Phase 3 Placebo-Controlled Studies (Baseline Pain VAS ≥ 70 : Week 14 LOCF Data)



Source: g_line_achieving specified PAIN reduction_baseline pain vas GE 70

Figure 12. Analysis of Change from Baseline in Pain VAS by Baseline Pain VAS: Phase 3 Placebo-Controlled Studies (Baseline Pain VAS ≥ 70 : LOCF Data)



4.3.9 Efficacy Conclusions

The efficacy of sodium oxybate in the treatment of fibromyalgia has been demonstrated in two adequate, well-controlled, 14-week, Phase 3 trials and is supported by the results of a well-controlled, 8 week, Phase 2 trial. In addition, efficacy was maintained for up to 52 weeks (including 14 weeks in the Phase 3 controlled trials) in an ongoing, 38-week, open-label extension of the Phase 3 trials. Across all four studies in which efficacy was assessed, sodium oxybate provided clinically important therapeutic benefits across multiple domains relevant to the assessment of fibromyalgia. Sodium oxybate, in 4.5 and 6 g/night doses, was effective in relieving pain, the hallmark symptom of fibromyalgia and the primary endpoint for the Phase 3 clinical trials. The levels of pain relief seen with both doses of sodium oxybate are moderate to substantial in magnitude. Sodium oxybate also reduced fatigue and improved functionality and sleep in subjects with fibromyalgia. Effects were seen as early as one week after treatment initiation and persisted throughout the study periods of the 14-week controlled trials and were maintained in the long-term, open-label trial. Notably, sodium oxybate provides relief of symptoms related to the core domains defined by OMERACT as important to patients: pain, tenderness, fatigue, sleep disturbance, patient global assessment, and multidimensional functionality.

The clinical program results for sodium oxybate in fibromyalgia are unique in that this is the first program in which efficacy for pain and functionality were demonstrated along with statistically significant and clinically meaningful improvements in fatigue and sleep disturbance in both pivotal trials ([Arnold et al. 2008](#), [Arnold et al. 2005](#), [Arnold et al. 2004](#), [Clauw et al. 2008](#), [Crofford et al. 2008](#), [Mease et al. 2009a](#), [Mease et al. 2008](#), [Russell et al. 2008](#)). The availability of sodium oxybate as an option for fibromyalgia patients is important for those whose fatigue and sleep disturbance are often as debilitating to them as their pain. Sodium oxybate may provide a solution to an unmet need for those who do not have a broad enough range of symptom relief from their current therapies, whose primary pain relief needs are not met by other approved agents, or who need a different tolerability profile.

Objective data on sleep measures, efficacy data from the Phase 2 and 3 studies in fibromyalgia, LOCF analyses that provide data particularly relevant to dose selection, and exploratory analysis demonstrate that the 4.5 and 6 g/night doses are the appropriate doses for patients with fibromyalgia. These data suggest that the 4.5 g/night dose provides benefit for a substantial portion of patients and that the 6 g/night dose offers additional benefit to patients with severe pain when warranted by individual patient need and tolerability.

4.4 Summary of Safety

4.4.1 Fibromyalgia Clinical Studies and Xyrem US Postmarketing Data

Data from the fibromyalgia clinical studies for treatment-emergent adverse events, serious adverse events, other safety data (ie, clinical laboratory tests, vital signs, body weight, BMI, and ECGs), and safety topics of special interest are summarized in this section. [Table 27](#) lists the pooled populations (with sample sizes) used for analyses of safety data summarized in this document. US postmarketing data for the commercial sodium oxybate product Xyrem are also summarized as appropriate. Data from the clinical trials with Xyrem are summarized in [Section 4.4.2](#).

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Table 27. Pooled Populations from Fibromyalgia Studies, All-Treated Populations

Populations for Pooled Analyses	Placebo	Sodium Oxybate Dose		All Sodium Oxybate
		4.5 g	6 g	
Phase 3 Placebo-Controlled Studies ^a (06-008 + 06-009)	371	376	371	747
Phase 2 and Phase 3 Placebo-Controlled Studies ^a (OMC-SXB-26 + 06-008 + 06-009)	436	436	438	874
Phase 2 and Phase 3 Studies (OMC-SXB-26 + 06-008 + 06-009 + 06-010)	N/A	N/A	N/A	1060
Phase 3 Studies, Subjects Who Rolled Over to Study 06-010 (06-008 + 06-009 + 06-010)	N/A	N/A	N/A	560

N/A=not applicable. All Sodium Oxybate patients were used in the analysis for this section.

Note: Data cutoff includes subject data from 06-010 through 02 September 2009 (database version, 15 December 2009) and incorporated errata from 06-008 and 06-009 (including adverse events first reported in 06-010 that had start dates in the prior studies).

^a Reflects numbers of subjects by randomized treatment.

4.4.1.1 Extent of Exposure

The Phase 2 and Phase 3 study population includes data from fixed-dose administration of sodium oxybate in the three short-term placebo-controlled studies and flexible-dose administration of sodium oxybate in the 38-week, open-label extension study 06-010 (in which the dose range was 4.5 to 9 g/night). In the two Phase 3 controlled studies, sodium oxybate was initiated at 4.5 g/night for all subjects randomized to active treatment. For subjects randomized to the 6 g/night group, sodium oxybate was maintained at 4.5 g/night for the first 2 weeks, then increased to 6 g/night.

Based on extensive postmarketing experience with sodium oxybate in patients with narcolepsy, the FDA allowed a reduced exposure requirement for the fibromyalgia population. Sodium oxybate exposure in the fibromyalgia and narcolepsy clinical programs and in postmarketing experience with Xyrem is summarized in [Table 28](#).

Table 28. Sodium Oxybate Exposure in Fibromyalgia Clinical Program, Narcolepsy Clinical Program, and Xyrem Postmarketing Experience

	Number of Subjects	Exposure (Subject-years)
Fibromyalgia Clinical Program		
Phase 2 and 3 Placebo-controlled Studies ^a	874	168
Phase 2 and 3 Studies ^b	1060	458
At least 26 weeks	397 (37.5%)	
At least 52 weeks	160 (15.1%)	
Narcolepsy Clinical Program	781	1106
Xyrem Postmarketing US Experience	~35,000	~31,645

^a Includes OMC-SXB-26, 06-008, and 06-009

^b Includes OMC-SXB-26, 06-008, 06-009, and open-label extension study 06-010

Sources: ISS 4-month update Tables 1.1.3.1, 1.1.4.1

Exposure by dose in Phase 2 and Phase 3 studies in fibromyalgia was 194 subject-years at 4.5 g, 172 subject-years at 6 g, 55 subject-years at 7.5 g and 34 subject-years at 9 g.

4.4.1.2 Demographic and Other Characteristics of Study Population

Demographic and fibromyalgia disease characteristics for subjects in the Phase 2 and Phase 3 placebo-controlled studies in fibromyalgia are summarized in [Sections 4.3.1.3](#) and [4.3.2.3](#).

4.4.1.3 Treatment-Emergent Adverse Events

Adverse events in all studies are summarized for all treated subjects. In the Phase 2 and Phase 3 placebo-controlled studies in fibromyalgia, safety data are summarized by randomized treatment. In the Phase 3 open-label extension study (06-010), adverse events are summarized by the dose the subject was taking at event onset.

Where applicable, adverse events from the postmarketing database for the commercial sodium oxybate product Xyrem are summarized and presented. A medical review of adverse events was conducted of both the fibromyalgia clinical program and the Xyrem postmarketing data. The numbers of subjects were combined for a few terms assessed as representing a common clinical phenomenon. Tables containing combined event terms are footnoted accordingly. Subsequent to the analysis of postmarketing events in this briefing document, we have identified a small number of additional postmarketing events that are currently under review and will be discussed in the presentation. All deaths have been reviewed and are included in this document.

The percentages of treatment-emergent adverse events occurring in Phase 2 and Phase 3 randomized controlled trials in fibromyalgia, including serious adverse events and discontinuations due to these events, are summarized in [Table 29](#).

Table 29. Summary of All Treatment-Emergent Adverse Events, Phase 2 and 3 Controlled Studies

Number (%) of Subjects	Placebo (n=436)	SXB 4.5 g (n=436)	SXB 6 g (n=438)	All SXB (n=874)
With Any AE	271 (62.2)	336 (77.1)	353 (80.6)	689 (78.8)
Discontinued due to AE	33 (7.6)	70 (16.1)	96 (21.9)	166 (19.0)
With Any SAE	4 (0.9)	3 (0.7)	6 (1.4)	9 (1.0)
Discontinued due to SAE	2 (0.5)	1 (0.2)	4 (0.9)	5 (0.6)

AE=adverse event, SAE=serious adverse event

Source: ISS 4-month update Table 4.4.3.1

PHASE 3 PLACEBO-CONTROLLED STUDIES

Most Frequent Adverse Events

Table 30 summarizes treatment-emergent adverse events that occurred in $\geq 2\%$ of subjects and greater than placebo in any treatment group in the Phase 3 placebo-controlled studies by descending order of frequency in the All Sodium Oxybate treatment group.

In the two Phase 3 controlled studies, sodium oxybate was initiated at 4.5 g/night for all subjects randomized to active treatment. For subjects randomized to the 6 g/night group, sodium oxybate was maintained at 4.5 g/night for the first 2 weeks, then increased to 6 g/night. Onset of adverse events reported by $\geq 5\%$ of subjects in any randomized treatment group in the Phase 2 and Phase 3 placebo-controlled studies was highest in the first 2 weeks after treatment initiation. New onset of most events decreased by at least one-half after the first 2 weeks (see [Table 32](#)).

Table 30. Summary of Most Frequent ($\geq 2\%$) Treatment-Emergent Adverse Events With Incidence Greater for Active Treatment than for Placebo by Preferred Term (With Combined Terms), Phase 3 Placebo-Controlled Studies

Number (%) of Subjects with AEs by Preferred Term	Placebo (N=371)	SXB 4.5 g (N=376)	SXB 6 g (N=371)	All SXB (N=747)
With Any AE	232 (62.5)	295 (78.5)	301 (81.1)	596 (79.8)
Nausea/vomiting ^a	33 (8.9)	68 (18.1)	89 (24.0)	157 (21.0)
Headache	56 (15.1)	69 (18.4)	85 (22.9)	154 (20.6)
Vertigo/dizziness ^a	12 (3.2)	54 (14.4)	66 (17.8)	120 (16.1)
Diarrhea	20 (5.4)	24 (6.4)	36 (9.7)	60 (8.0)
Nasopharyngitis/pharyngolaryngeal pain ^a	20 (5.4)	26 (6.9)	31 (8.4)	57 (7.6)
Anxiety	5 (1.3)	22 (5.9)	25 (6.7)	47 (6.3)
Nasal congestion/sinusitis ^a	9 (2.4)	22 (5.9)	19 (5.1)	41 (5.5)
Insomnia	10 (2.7)	18 (4.8)	17 (4.6)	35 (4.7)
Somnolence	12 (3.2)	12 (3.2)	19 (5.1)	31 (4.1)
Loss of appetite ^b /decreased appetite ^a	3 (0.8)	16 (4.3)	14 (3.8)	30 (4.0)
Fatigue	9 (2.4)	10 (2.7)	19 (5.1)	29 (3.9)
Muscle spasms	6 (1.6)	15 (4.0)	14 (3.8)	29 (3.9)
Paresthesia	5 (1.3)	12 (3.2)	14 (3.8)	26 (3.5)

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Table 30. Summary of Most Frequent (≥2%) Treatment-Emergent Adverse Events With Incidence Greater for Active Treatment than for Placebo by Preferred Term (With Combined Terms), Phase 3 Placebo-Controlled Studies

Number (%) of Subjects with AEs by Preferred Term	Placebo (N=371)	SXB 4.5 g (N=376)	SXB 6 g (N=371)	All SXB (N=747)
Back pain	7 (1.9)	10 (2.7)	15 (4.0)	25 (3.3)
Pain in extremity	9 (2.4)	12 (3.2)	12 (3.2)	24 (3.2)
Blood pressure increased/ blood pressure diastolic increased/blood pressure systolic increased/hypertension ^a	5 (1.3)	8 (2.1)	16 (4.3)	24 (3.2)
Depression/depressed mood ^a	5 (1.3)	7 (1.9)	12 (3.2)	19 (2.5)
Edema peripheral	7 (1.9)	5 (1.3)	15 (4.0)	20 (2.7)
Fibromyalgia	7 (1.9)	8 (2.1)	9 (2.4)	17 (2.3)
Constipation	6 (1.6)	9 (2.4)	8 (2.2)	17 (2.3)
Weight decreased	1 (0.3)	9 (2.4)	8 (2.2)	17 (2.3)
Arthralgia	4 (1.1)	10 (2.7)	7 (1.9)	17 (2.3)
Rash	8 (2.2)	6 (1.6)	10 (2.7)	16 (2.1)
Vision blurred	2 (0.5)	6 (1.6)	8 (2.2)	14 (1.9)
Urinary tract infection	5 (1.3)	9 (2.4)	5 (1.3)	14 (1.9)
Dry mouth	3 (0.8)	3 (0.8)	9 (2.4)	12 (1.6)
Hyperhidrosis	2 (0.5)	2 (0.5)	9 (2.4)	11 (1.5)
Pruritus	5 (1.3)	8 (2.1)	3 (0.8)	11 (1.5)
Disturbance in attention	1 (0.3)	8 (2.1)	2 (0.5)	10 (1.3)

AE=adverse event, SXB=sodium oxybate

^a Terms were assessed as representing a common clinical phenomenon; the numbers of subjects have been combined for these terms.

^b Loss of appetite includes the term anorexia

Note: This table includes data from Studies 06-008 and 06-009. Adverse events were coded using MedDRA version 9.1. Adverse events are summarized by randomized treatment. Combined preferred terms were not included in the sodium oxybate 4-month safety update.

Note: Data cutoff (database version, 15 December 2009) incorporated errata from 06-008 and 06-009 (including adverse events first reported in 06-010 that had start dates in the prior studies).

Source: ISS 4-month update Table 4.7.1 and database

Adverse Events Leading to Study Discontinuation

Adverse events that led to study discontinuation in ≥1% subject in any treatment group in the Phase 3 placebo-controlled studies are summarized in [Table 31](#).

Table 31. Summary of Treatment-Emergent Adverse Events Leading to Study Discontinuation in $\geq 1\%$ Subject in Any Treatment Group by Preferred Term (With Combined Terms), Phase 3 Placebo-Controlled Studies

Number (%) of Subjects with AEs by Preferred Term	Placebo (N=371)	SXB 4.5 g (N=376)	SXB 6 g (N=371)	All SXB (N=747)
With Any AE Leading to Study Discontinuation	30 (8.1)	64 (17.0)	81 (21.8)	145 (19.4)
Nausea/vomiting ^a	2 (0.5)	13 (3.5)	19 (5.1)	32 (4.3)
Headache	0	5 (1.3)	16 (4.3)	21 (2.8)
Vertigo/dizziness ^a	0	6 (1.6)	13 (3.5)	19 (2.5)
Anxiety	2 (0.5)	4 (1.1)	10 (2.7)	14 (1.9)
Insomnia	2 (0.5)	6 (1.6)	5 (1.3)	11 (1.5)
Diarrhea	0	2 (0.5)	8 (2.2)	10 (1.3)
Fatigue	1 (0.3)	3 (0.8)	6 (1.6)	9 (1.2)
Depression/depressed mood ^a	4 (1.1)	1 (0.3)	6 (1.6)	7 (0.9)
Somnolence	3 (0.8)	1 (0.3)	6 (1.6)	7 (0.9)
Blood pressure increased/ blood pressure diastolic increased/blood pressure systolic increased/hypertension ^a	2 (0.5)	1 (0.3)	4 (1.1)	5 (0.7)
Confusional state	1 (0.3)	1 (0.3)	4 (1.1)	5 (0.7)
Fibromyalgia	0	1 (0.3)	4 (1.1)	5 (0.7)
Feeling jittery	0	0	4 (1.1)	4 (0.5)

AE=adverse event, SXB=sodium oxybate

^a Terms were assessed as representing a common clinical phenomenon; the numbers of subjects have been combined for these terms.

Note: This table includes data from Studies 06-008 and 06-009. Adverse events were coded using MedDRA version 9.1. Adverse events are summarized by randomized treatment. Combined preferred terms were not included in the sodium oxybate 4-month safety update.

Note: Data cutoff (database version, 15 December 2009) incorporated errata from 06-008 and 06-009 (including adverse events first reported in 06-010 that had start dates in the prior studies).

Source: ISS 4-month update Table 4.12.1.1 and database

TIME TO ONSET OF ADVERSE EVENTS

Onset of adverse events reported in $\geq 5\%$ of subjects in any randomized treatment group in the Phase 2 and Phase 3 placebo-controlled studies, including headache, nausea, dizziness, diarrhea, vomiting, anxiety, insomnia, and somnolence, for subjects randomized to sodium oxybate treatment was highest in the first 2 weeks after treatment initiation. Incidence of new onset decreased by at least one-half from the first 2 weeks following treatment initiation to the next 2 weeks for all of these events except for vomiting and anxiety. Nasopharyngitis was the only adverse event reported in $\geq 5\%$ of subjects that had the highest rate of onset during Weeks 3 to 4 following sodium oxybate treatment initiation.

Table 32. Treatment-Emergent Adverse Events with Incidence \geq 5% for Any Treatment Group by Time of Onset, Total and Weeks 1-4, Subjects Randomized to Active Treatment in the Phase 2 and 3 Controlled Trials

Number (%) of Subjects with	Total (n=874)	Time of Onset	
		Weeks 1-2 (n=874)	Weeks 3-4 (n=768)
Headache	173 (19.8)	124 (14.2)	34 (4.4)
Nausea	172 (19.7)	113 (12.9)	38 (4.9)
Dizziness	120 (13.7)	86 (9.8)	24 (3.1)
Diarrhea	64 (7.3)	38 (4.3)	12 (1.6)
Vomiting	62 (7.1)	34 (3.9)	18 (2.3)
Nasopharyngitis	53 (6.1)	15 (1.7)	16 (2.1)
Anxiety	51 (5.8)	18 (2.1)	10 (1.3)
Insomnia ^a	41 (4.7)	31 (3.5)	5 (0.7)
Somnolence ^b	36 (4.1)	30 (3.4)	6 (0.8)

Note: This table reports the number of subjects with new onset of treatment-emergent adverse events during Weeks 1-2 and Weeks 3-4. Subjects who only had onset of these adverse events after Week 4 are reported in the total column only.

^a Insomnia had incidence \geq 5% for the sodium oxybate 4.5 g group only

^b Somnolence had incidence \geq 5% for the sodium oxybate 6 g group only

LONG-TERM ADVERSE EVENT DATA

Most Frequent Adverse Events

Treatment-emergent adverse events reported by \geq 5% in any sodium oxybate treatment group or overall and that occurred in the subset of subjects who participated in either 06-008 or 06-009 and subsequently enrolled in 06-010 (i.e., all Phase 3 studies) are summarized in Table 33. The corresponding duration of exposure in this subset of subjects was up to 52 weeks (14 weeks randomized treatment [Placebo, Sodium Oxybate 4.5 g, or Sodium Oxybate 6 g] in placebo-controlled studies plus up to 38 weeks exposure in the flexible-dose, open-label extension study [Sodium Oxybate 4.5 to 9 g]).

Table 33. Treatment-Emergent Adverse Events Reported by \geq 5% in Any Dose Group or Overall by Preferred Term, Phase 3 Studies—Subjects Who Rolled Over to Study 06-010

Number (%) of Subjects with AEs	SXB 4.5 g (N=550)	SXB 6 g (N=461)	SXB 7.5 g (N=238)	SXB 9 g (N=112)	All SXB ^a (N=560)
Any AE	359 (65.3)	334 (72.5)	159 (66.8)	88 (78.6)	516 (92.1)
Headache	72 (13.1)	72 (15.6)	20 (8.4)	6 (5.4)	151 (27.0)
Nausea	64 (11.6)	71 (15.4)	23 (9.7)	10 (8.9)	146 (26.1)
Dizziness	46 (8.4)	50 (10.8)	13 (5.5)	6 (5.4)	108 (19.3)
Diarrhea	28 (5.1)	35 (7.6)	7 (2.9)	3 (2.7)	70 (12.5)
Nasopharyngitis	27 (4.9)	32 (6.9)	7 (2.9)	5 (4.5)	68 (12.1)
Vomiting	27 (4.9)	26 (5.6)	9 (3.8)	6 (5.4)	64 (11.4)
Sinusitis	27 (4.9)	24 (5.2)	13 (5.5)	4 (3.6)	63 (11.3)
Anxiety	28 (5.1)	24 (5.2)	11 (4.6)	3 (2.7)	55 (9.8)
Influenza	16 (2.9)	19 (4.1)	9 (3.8)	3 (2.7)	46 (8.2)

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Table 33. Treatment-Emergent Adverse Events Reported by ≥5% in Any Dose Group or Overall by Preferred Term, Phase 3 Studies—Subjects Who Rolled Over to Study 06-010

Number (%) of Subjects with AEs	SXB 4.5 g (N=550)	SXB 6 g (N=461)	SXB 7.5 g (N=238)	SXB 9 g (N=112)	All SXB ^a (N=560)
Upper respiratory tract infection	11 (2.0)	21 (4.6)	11 (4.6)	4 (3.6)	44 (7.9)
Somnolence	15 (2.7)	22 (4.8)	3 (1.3)	6 (5.4)	42 (7.5)
Muscle spasms	14 (2.5)	16 (3.5)	10 (4.2)	4 (3.6)	42 (7.5)
Insomnia	14 (2.5)	17 (3.7)	10 (4.2)	3 (2.7)	41 (7.3)
Fatigue	14 (2.5)	14 (3.0)	7 (2.9)	1 (0.9)	35 (6.3)
Urinary tract infection	13 (2.4)	12 (2.6)	4 (1.7)	6 (5.4)	33 (5.9)
Pain in extremity	18 (3.3)	12 (2.6)	7 (2.9)	2 (1.8)	33 (5.9)
Arthralgia	12 (2.2)	15 (3.3)	3 (1.3)	3 (2.7)	31 (5.5)
Weight decreased	11 (2.0)	14 (3.0)	3 (1.3)	2 (1.8)	30 (5.4)
Back pain	15 (2.7)	12 (2.6)	2 (0.8)	0	29 (5.2)
Gastroenteritis viral	2 (0.4)	5 (1.1)	5 (2.1)	6 (5.4)	18 (3.2)

AE=adverse event, SXB=sodium oxybate

Note: This table includes data from Studies 06-008, 06-009, and 06-010. Adverse events were coded using MedDRA version 9.1. Adverse events that occurred during Studies 06-008 and 06-009 are summarized by randomized treatment, and adverse events that occurred during Study 06-010 are summarized by dose at onset.

Note: Data cutoff includes subject data from 06-010 through 02 September 2009 (database version, 15 December 2009) and incorporated errata from 06-008 and 06-009 (including adverse events first reported in 06-010 that had start dates in the prior studies).

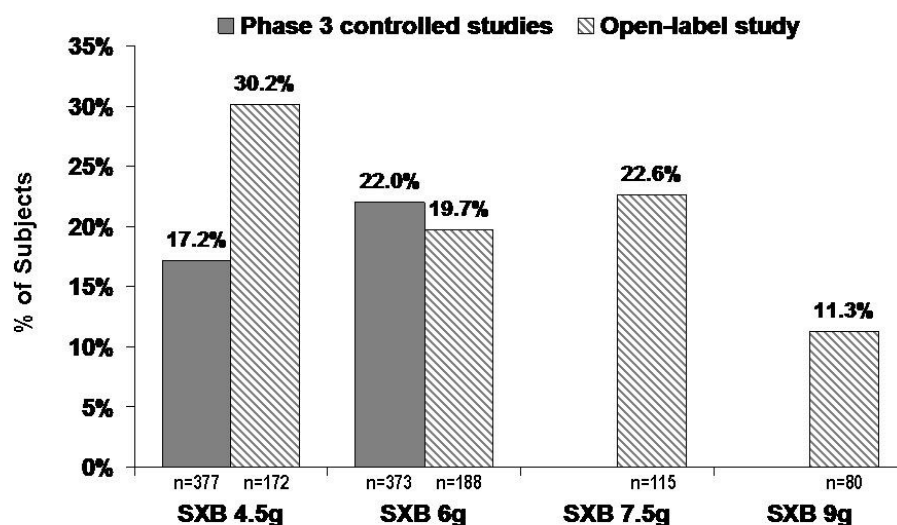
^a If the dose at adverse event onset in 06-010 was not among the indicated doses, the subject was summarized in the All SXB group only.

Source: ISS 4-month update Table 4.5.5.1

Adverse Events Leading to Study Discontinuation

The percentages of subjects who discontinued for an adverse event from Phase 3 placebo-controlled and open-label studies are displayed and compared by dose group in [Figure 13](#). The percentage of subjects who discontinued at the 4.5 g dose was greater in the open-label trial than in the controlled trials. In the open-label trial, of those patients who discontinued for adverse events on the 4.5 g dose, a greater percentage had been randomized to placebo than to either active treatment in the prior controlled trials. The percentages of subjects who discontinued at the 6 g dose were similar in the open-label and controlled trials.

Figure 13. Percentage of Subjects Who Discontinued from Studies due to Adverse Events, Phase 3 Controlled Studies and Open-Label Study 06-010



Phase 3 controlled studies include study 06-008 and 06-009; open-label study includes 06-010

Source: ISS 4-month update Table 3.1.2 and database (06-010 data)

DEATHS AND OTHER SERIOUS ADVERSE EVENTS

There were no deaths in any of the fibromyalgia clinical trials. Overall, 26 of 1060 (2.5%) sodium oxybate-treated subjects experienced at least one treatment-emergent serious adverse event in Phase 2 and 3 trials (Table 34). Of these, six subjects had serious adverse events considered related to study treatment (Table 35 and Table 37). Four of these six subjects had one or more serious adverse events (vomiting, sleep paralysis, unresponsive to stimuli, headache, and gastrointestinal hypomotility) considered related to treatment, all of which led to study discontinuation. A fifth subject had treatment-related serious adverse events of accidental overdose and encephalopathy that led to interruption of study drug dosing; the subject was restarted on study drug without incident. A sixth subject had a serious adverse event of bipolar disorder that the investigator assessed as unrelated to treatment; the sponsor could not rule out a possible relationship to treatment. One subject experienced a serious adverse event, cervical spinal stenosis, at two different times in Studies 06-009 and 06-010, respectively.

Table 34. Summary of Treatment-Emergent Serious Adverse Events

Number (%) of Subjects	Placebo (N=436)	All Sodium Oxybate (N=1060)
With Any SAE	4 (0.9%)	26 ^a (2.5%)
Discontinued due to SAEs	2 (0.5%)	10 (0.9%)

^a One subject experienced the same serious adverse event, cervical spinal stenosis, at two different times in Study 06-009 and 06-010, respectively.

Source: ISS 4-month update Tables 4.4.3.1 and 4.4.4.1

Phase 2 and Phase 3 Placebo-Controlled Studies (OMC-SXB-26, 06-008, and 06-009)

In the Phase 2 and Phase 3 placebo-controlled studies, 9 of 874 sodium oxybate-treated subjects (1.0%) had at least one treatment-emergent serious adverse event. The percentages of subjects experiencing serious adverse events across the randomized treatment groups were 0.9% (4 subjects) in the placebo group, 0.7% (3 subjects) in the Sodium Oxybate 4.5 g group, 1.4% (6 subjects) in the Sodium Oxybate 6 g group, and 1.0% (9 subjects) in the All Sodium Oxybate group.

Four subjects with serious adverse events occurring in Phase 2 and 3 controlled studies that were considered to be related to sodium oxybate are presented in Table 35. The table is followed by brief descriptions of these cases. In this analysis population, no serious adverse event preferred term was reported in more than one subject in any treatment group or in the All Sodium Oxybate group.

Table 35. Treatment-Emergent Related Serious Adverse Events, All-Treated Population, Phase 2 and Phase 3 Placebo-Controlled Studies

Study (Age [y], Gender, Race)	Serious Adverse Event(s) ^a	Treat- ment Group	Start–Stop (Study Day)	Severity	Relation- ship ^b	Change in Drug/Study Participation ^c	Outcome
06-009 (47, F, W)	Vomiting	4.5 g	1–2	Severe	Related	Study DCd	Resolved
06-008 (35, F, W)	Sleep paralysis	6 g	1–1	Severe	Related	Study DCd	Resolved
	Unresponsive to stimuli		1–2	Moderate	Related	Study DCd	Resolved
06-009 (60, F, W)	Headache	6 g	25Jun (Day 29)– Aug 2008	Moderate	Related	Study DCd	Resolved
OMC- SXB-26 (61, F, W)	Tachycardia	6 g	13– ongoing	Moderate	Not Related	Study DCd	Not Resolved
	Bipolar disorder		13–30	Severe	Not Related ^d	Study DCd	Resolved
	Hypertension		13– ongoing	Moderate	Not Related	Study DCd	Not Resolved

B=Black or African American, DCd=discontinued, F=female, FDA=US Food and Drug Administration, IND=Investigational New Drug Application, M=male, O=Other (not Black/African American/White), W=White

^a MedDRA preferred term

^b Relationship to study drug or procedure

^c Drug DCd indicates discontinuation or interruption of study drug dosing. Study DCd indicates discontinuation of study participation.

^d Bipolar disorder was considered not related to the study drug by the investigator, however, sponsor (Orphan Medical) could not rule out the possibility that bipolar disorder may have been related to study treatment and submitted this case to the FDA as a 15-day IND safety report.

Source: ISS 4-month update Table 4.3

- One subject, randomized to Sodium Oxybate 4.5 g in Study 06-009, had a 3-week history of bilateral otitis prior to study initiation. Bilateral otitis was treated with erythromycin and ciprofloxacin but with no relief. On the first day of her starting her study drug, the

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subject started treatment of levofloxacin for her otitis. Eight hours after she took her 1st dose of levofloxacin, she took her very 1st dose of study drug at 2.25 g. Twenty minutes later, the subject began vomiting repeatedly. She was then taken to an emergency department, where she was hydrated and received IV metoclopramide and famotidine. Event resolved on the same day and study drug was discontinued.

- One subject was randomized to Sodium Oxybate 6 g in Study 06-008. On Day 1, approximately 45 minutes after her very first dose of 2.25 g study drug, the subject had sleep paralysis. Sleep paralysis resolved after 30 minutes. After the resolution of sleep paralysis, the subject began to vomit and crawled to the bathroom where she had nausea, vomiting, diarrhea, and profound muscular weakness. The subject fell off the toilet. Approximately 4 hours later, the subject woke up on the bathroom floor as her daughter was dabbing her with cold water. The daughter had been trying to awaken her for an unknown period of time. Upon awakening, this subject experienced dyspnea, described as labored breathing similar to hyperventilating and had trouble inhaling deeply. Other temporally associated adverse events included amnesia, hyperhidrosis, cyanosis, abdominal discomfort, asthenia, chest pain, chills, fatigue, tremor, throat irritation, and cold sweat. Many of the adverse events experienced by this subject were assessed as related to study drug by the investigator. She received no further doses of sodium oxybate and was discontinued from the study. Most events resolved within 1 to 2 days; however, the nausea, abdominal discomfort, and chest pain resolved after 4 days and the asthenia and fatigue resolved after 2 weeks.
- One subject was randomized to Sodium Oxybate 6 g in Study 06-009. On Day 29, the subject developed intermittent headache. Last dose of study drug was taken on Day 33. The subject's headache persisted after study drug discontinuation. The subject was hospitalized to rule out any organic causes for her headache. No significant findings were revealed. The subject was discharged. Headache resolved approximately 1 month after discharging from hospital and 2 month after the onset. Concurrent adverse events included swollen hands (Day 16–ongoing), blood pressure increased (Days 16–34), tingling hands (Days 16–ongoing), and conjunctivitis (Days 23–31).
- One subject was randomized to Sodium Oxybate 6 g in Study OMC-SXB-26. Approximately after 13 days of nightly dosing with sodium oxybate the subject began “acting out of character” and had increasing agitation with violent and abusive behavior. The subject stopped taking study drug 5 days after the event started. The following night, the subject was hospitalized due to a manic episode with psychotic features. The investigator considered the event as not related to the study drug, however, the sponsor could not rule out a possible relationship.

Subjects with serious adverse events that were not considered related to the study drug in Phase 2 and Phase 3 placebo-controlled studies are listed in Table 36.

Table 36. Treatment-Emergent Not Related Serious Adverse Events, All-Treated Population, Phase 2 and Phase 3 Placebo-Controlled Studies

Study (Age [y], Gender, Race)	Serious Adverse Event(s) ^a	Treatment Group	Start–Stop (Study Day)	Severity	Relationship ^b	Change in Drug/Study Participation ^c	Outcome
06-009 (37, F, W)	Inguinal hernia	4.5 g	73–102	Severe	Not Related	Drug DCd	Resolved
OMC-SXB-26 (37, F, W)	Respiratory tract infection	4.5 g	29–ongoing	Severe	Not Related	Drug DCd	Not Resolved
	Asthma		29–36	Severe	Not Related	Drug DCd	Resolved
06-008 (51, F, W)	Large intestine perforation	6 g	25–38	Severe	Not Related	Study DCd	Resolved
	Abscess intestinal		25–38	Severe	Not Related	Drug DCd	Resolved
	Diverticulitis		25–38	Severe	Not Related	Drug DCd	Resolved
06-009 (44, F, B)	Rotator cuff syndrome	6 g	25–112	Moderate	Not Related	Drug DCd	Resolved w/ sequelae
06-009 (58, F, W)	Cervical spinal stenosis	6 g	Jun–Jul 2008	Mild	Not Related	No Change	Resolved
06-008 (51, F, O)	Colitis	Placebo	88–105	Moderate	Not Related	Study DCd	Resolved
06-009 (63, F, B)	Musculo-skeletal pain	Placebo	8–9	Moderate	Not Related	Drug DCd	Resolved
06-009 (36, F, B)	Contusion	Placebo	15–ongoing	Moderate	Not Related	Drug DCd	Unknown
	Joint sprain		15–ongoing	Moderate	Not Related	Drug DCd	Unknown
	Scratch		15–ongoing	Moderate	Not Related	Drug DCd	Unknown
06-009 (52, F, W)	Secondary hypertension	Placebo	35–67	Severe	Not Related	Study DCd	Resolved

B=Black or African American, DCd=discontinued, F=female, FDA=US Food and Drug Administration, IND=Investigational New Drug Application, M=male, O=Other (not Black/African American/White), W=White

^a MedDRA preferred term

^b Relationship to study drug or procedure

^c Drug DCd indicates discontinuation or interruption of study drug dosing. Study DCd indicates discontinuation of study participation.

Source: ISS 4-month update Table 4.3

Phase 3 Long-term Open-label Study (06-010)

In the Phase 3 long-term open-label study, 19 of 560 sodium oxybate-treated subjects (3.3%) had at least one treatment-emergent serious adverse event. The percentages of subjects experiencing serious adverse events across the treatment groups were 1.3% (7 subjects) in the

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SXB 4.5 g group, 0.9% (5 subjects) in the SXB 6 g group, 0.2% (1 subject) in the SXB 7.5 g group, and 1.1% (6 subjects) in the SXB 9 g group.

Two subjects with serious adverse events occurring in the open-label study that were considered to be related to sodium oxybate are presented in Table 37. The table is followed by brief descriptions of these cases.

Table 37. Treatment-Emergent Related Serious Adverse Events, All-Treated Population, Phase 3 Long-term Open-label Study

Study (Age [y], Gender, Race)	Serious Adverse Event(s) ^a	Treat- ment Group	Start–Stop (Study Day)	Severity	Relation- ship ^b	Change in Drug/Study Participation ^c	Outcome
06-010 (46, F, O)	Accidental overdose	9 g	171–172	Severe	Related	Drug DCd	Resolved
	Encephalopathy		171–172	Severe	Related	Drug DCd	Resolved
06-010 (55, F, W)	Gastrointestinal hypomotility	9 g	146–154	Moderate	Related	Study DCd	Resolved

B=Black or African American, DCd=discontinued, F=female, FDA=US Food and Drug Administration, IND=Investigational New Drug Application, M=male, O=Other (not Black/African American/White), W=White

^a MedDRA preferred term

^b Relationship to study drug or procedure

^c Drug DCd indicates discontinuation or interruption of study drug dosing. Study DCd indicates discontinuation of study participation.

Source: ISS 4-month update Table 4.3

- One subject was receiving study drug at 9 g/night. On Day 171, after taking her 1st half nightly dose of 4.5 g, the subject accidentally took 9 g for her 2nd half dose instead of 4.5 g. Three hours later, the subject was found to be unresponsive. The subject was brought to an emergency department. Eight hours after the 2nd dose, the subject woke up at the hospital and fully recovered. The subject was discharged with a diagnosis of toxic encephalopathy due to accidental overdose of the study drug. Study drug was later resumed as the investigator felt that the subject was safe to continue the study.
- One subject, with medical history of diabetes, gastroesophageal reflux disorder (GERD), and ulcerative colitis developed abdominal pain with vomiting and chills on Day 146. The subject was receiving 9 g study per night at the time. The last dose was taken on Day 146. The subject was admitted to the hospital and was diagnosed with pseudo-obstruction of the small bowel. The event resolved 7 days after the onset and the last dose of the study drug.

Serious adverse events that were not considered related to the study drug in Phase 3 long-term open-label study are listed in Table 38.

Table 38. Treatment-Emergent Not Related Serious Adverse Events, All-Treated Population, Phase 3 Long-term Open-label Study

Study (Age [y], Gender, Race)	Serious Adverse Event(s) ^a	Treatment Group	Start–Stop (Study Day)	Severity	Relationship ^b	Change in Drug/Study Participation ^c	Outcome
06-010 (51, F, W)	Breast cancer in situ	4.5 g	2008–08Nov2008 (Day 251)	Severe	Not Related	No Change	Resolved
06-010 (57, F, B)	Cholelithiasis	4.5 g	2008–12Apr2008 (Day 158)	Moderate	Not Related	No Change	Resolved
	Cholecystitis chronic		2008–12Apr2008 (Day 158)	Moderate	Not Related	No Change	Resolved
06-010 (55, F, W)	Atrial fibrillation	4.5 g	169–170	Severe	Not Related	No Change	Resolved
06-010 (57, M, W)	Chest pain	4.5 g	3–6	Moderate	Not Related	Not Applicable (but drug interrupted)	Resolved
06-010 (58, F, W)	Cervical spinal stenosis	4.5 g	79–188	Mild	Not Related	No Change	Resolved
06-010 (59, M, W)	Arteriosclerosis	4.5 g	7–8	Severe	Not Related	Drug DCd	Resolved w/ sequelae
	Staphylococcal sepsis		8–102	Severe	Not Related	Study DCd	Resolved w/ sequelae
06-010 (64, F, W)	Chest pain	4.5 g	4–5	Moderate	Not Related	No Change	Resolved
06-010 (39, F, W)	Diverticulitis	6 g	97–102	Severe	Not Related	No Change	Resolved w/ sequelae
06-010 (24, F, W)	Abdominal pain	6 g	35–38	Moderate	Not Related	Study DCd	Resolved
06-010 (41, F, W)	Endometriosis	6 g	Jan2008–26Jun2008 (Day 206)	Moderate	Not Related	No Change	Resolved
06-010 (41, F, W)	Clostridium difficile colitis	9 g	200–206	Moderate	Not Related	No Change	Resolved
06-010 (45, M, W)	Accident	6 g	40–ongoing	Severe	Not Related	No Change	Resolving
06-010 (54, F, W)	Ovarian cyst	6 g	65–65	Severe	Not Related	Drug DCd	Resolved

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Table 38. Treatment-Emergent Not Related Serious Adverse Events, All-Treated Population, Phase 3 Long-term Open-label Study

Study (Age [y], Gender, Race)	Serious Adverse Event(s) ^a	Treat- ment Group	Start–Stop (Study Day)	Severity	Relation- ship ^b	Change in Drug/Study Participation ^c	Outcome
06-010 (44, F, W)	Cholecystitis acute	7.5 g	160–162	Severe	Not Related	No Change	Resolved
06-010 (61, F, W)	Cholelithiasis	9 g	100–101	Severe	Not Related	Drug DCd	Resolved
06-010 (62, F, W)	Chronic obstructive pulmonary disease	9 g	258–265	Severe	Not Related	Study DCd	Resolved w/ sequelae
06-010 (27, M, O)	Mental disorder	9 g	147– ongoing	Severe	Not Related	Study DCd	Unknown

B=Black or African American, DCd=discontinued, F=female, IND=Investigational New Drug Application, M=male, O=Other (not Black/African American/White), W=White

^a MedDRA preferred term

^b Relationship to study drug or procedure

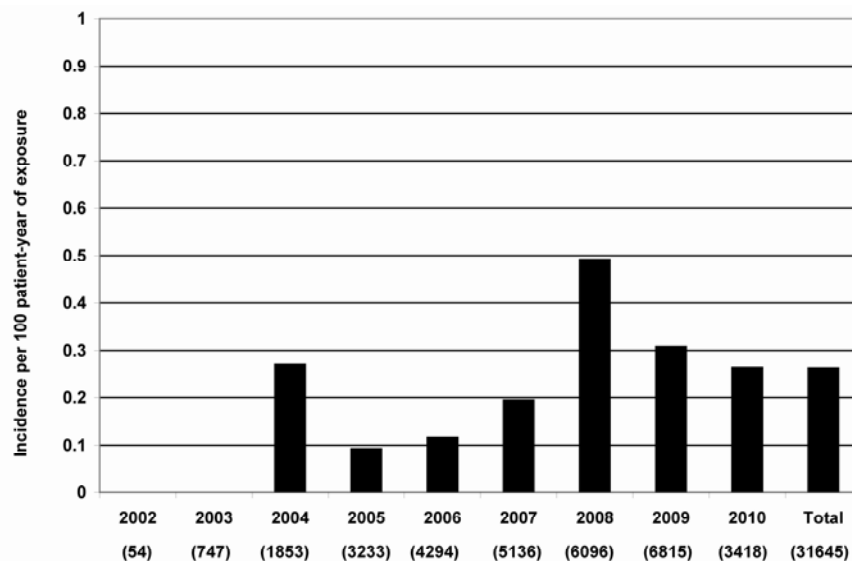
^c Drug DCd = discontinuation or interruption of study drug dosing. Study DCd = discontinuation of study participation.

Source: ISS 4-month update Table 4.3

Xyrem Postmarketing Experience

The commercial product Xyrem was introduced in 2002 and was acquired by Jazz Pharmaceuticals in 2005. A new indication was added in late 2005, and patient exposure has gradually increased over time (estimated total exposure of 31,645 patient-years). Figure 14 presents the rate of deaths per 100 patient-years of exposure over time to allow a view of the rate of death independent of changes in exposure. Overall, although numbers of deaths have varied from year to year, the rate has remained relatively stable over time.

Figure 14 Incidence of Death per 100 Patient-Years of Exposure over Time: Xyrem Postmarketing Experience



Note: The numbers in the parentheses are the numbers of patient-years of exposure for the given year.

Note: The incidence of death for the partial year 2010 can be directly compared to the other data since all the data are normalized to 100 patient-years.

In total, there were 83 deaths in the United States since market introduction in 2002. Causes of deaths in the postmarketing experience with Xyrem are summarized by category in [Table 39](#). Deaths are included regardless of whether Xyrem was or was not implicated as a cause. These events were placed in four broad categories: those involving overdose, those involving suicide, those where other medical cause(s) was identified, and those where no cause was identified. For detailed information about overdoses and suicides in postmarketing experience, see [Section 4.4.1.5](#), Suicide and Overdose subsections. For a listing of all postmarketing deaths, see [Appendix E](#).

Table 39 Causes of Death by Cause from Postmarketing Experience with Xyrem

Cause	Number of Cases	Incidence per 100 Patient-Years of Exposure
Overdose	4	0.013
Suicide	6	0.019
Other medical cause identified	29	0.092
Cause unidentified	44	0.139
Total	83	0.262

PREGNANCIES

In the fibromyalgia program, six pregnancies occurred during the Phase 2 and Phase 3 studies. Three of the six pregnancies ended in spontaneous abortions, all of which were considered unrelated to study treatment by the investigator. The fourth pregnancy was terminated by elective abortion. The remaining two pregnancies resulted in live births, and the infants are reported as doing well. Short descriptions of the six pregnancies follow.

- A 27-year-old subject, who was randomized to Sodium Oxybate 6 g/night in Study OMC-SXB-26, was discontinued from the study due to pregnancy. Although the subject had a negative urine pregnancy test on Day 1, a home pregnancy test was positive on Day 5. A serum pregnancy test done at early termination was positive. She had reportedly been using condoms and spermicidal foam routinely. On follow-up it was learned that the subject had an elective abortion due to a family situation. Because of nausea after the first dose, the subject had taken only one dose of study medication nightly from Day 1 to Day 5.
- A 26-year-old subject, who was randomized to Sodium Oxybate 6 g nightly in Study 06-009, became pregnant and was discontinued from the study. The subject had negative urine pregnancy tests on Days 1 and 32 of the study. On Day 49 the subject took a home pregnancy test that showed a positive result, which was confirmed by a urine and serum pregnancy test. The last dose of study drug was taken on Day 49, and the subject was discontinued from the study on Day 50. The subject began experiencing spotting and cramping 15 days after the last dose of study drug and a spontaneous abortion occurred 3 days later. Test results for *Chlamydia*, gonorrhea, and HIV were negative. Pathology examination showed no gestational products. Her medical history was significant for three prior pregnancies resulting in two viable births and one miscarriage that occurred 4 months prior to initiating dosing in this study. She reported no family history of miscarriage and denied any high risk behaviors.
- A 24-year-old subject, who previously completed Study 06-008 in the Sodium Oxybate 6g treatment group while receiving Sodium Oxybate 9 g nightly in Study 06-010, became pregnant and withdrew consent to further study participation. On Day 1 of Study 06-010 the subject's urine pregnancy test was negative. On Day 252 the subject had a positive pregnancy test and an ultrasound on the same date showed that she was approximately 11 weeks pregnant. Study drug was discontinued, and the subject discontinued from the study on Day 255. Approximately 6 months later the infant was born by Cesarean

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section. No complications were reported. The subject had been taking Yasmin (drospirenone 3 mg and ethinyl estradiol 0.030 mg) daily for birth control.

- A 36-year-old subject, who previously completed Study 06-008 in the Sodium Oxybate 6 g treatment group, was receiving 7.5 g nightly in Study 06-010 when she was discontinued from the study due to pregnancy. On Day 1 her urine pregnancy test was negative. On Day 72 she reported that she had missed her period for 2 weeks. On this same day a urine pregnancy test was found to be positive, and the subject was discontinued from the study. A spontaneous abortion occurred approximately 10 days later. At the follow-up study visit 5 days later she was found to be in good health. The subject reported using condoms and spermicidal gel during the study. Her medical history was significant for three Cesarean sections and a tubal ligation performed approximately 2 years prior to study entry. The subject was a non-smoker and had no sexually transmitted diseases.
- A 23-year-old subject, who previously had completed Study 06-009 in the 6 g treatment group, was receiving Sodium Oxybate 4.5 g nightly in Study 06-010 when she was discontinued from the study for a serious adverse event of abortion spontaneous (verbatim term: spontaneous abortion). The subject completed Study 06-009 and was enrolled in Study 06-010 at the same study visit. At this visit a urine pregnancy test was negative and a serum pregnancy test was also taken and sent to a central lab. The subject was already enrolled in Study 06-010 and had dosed for 3 days when the site learned that the serum pregnancy test was positive. The subject was immediately discontinued from the study and had a spontaneous abortion approximately 2.5 weeks after discontinuing study drug. Based on ultrasound data, the pregnancy occurred during the previous study. The subject had reported that she would use abstinence during the study. The subject's medical history was non-contributory.
- A 37-year-old subject became pregnant during Study 06-009 while receiving Sodium Oxybate 6 g nightly. She was enrolled in Study 06-010 and receiving 7.5 g nightly when the pregnancy was discovered. On Day 1 of Study 06-010 the subject had both a negative urine pregnancy test and a negative serum pregnancy test. On Day 53 the subject had a positive pregnancy test, was estimated to be 10 weeks pregnant, and was discontinued from the study. A male infant was delivered by Cesarean section about 7.5 months after study discontinuation. The Cesarean section was performed due to 2-3 fetal heart rate decelerations. A follow-up report stated that the subject and infant were doing well. The subject reported using abstinence as a birth control method during both studies. The subject had an obstetrical history of gravida 2 with 2 elective abortions; other medical history was non-contributory.

4.4.1.4 Other Safety Evaluations

To provide a longitudinal analysis of safety data, data from controlled studies 06-008 and 06-009 have been combined with data from the open-label extension study 06-010, and visits in 06-010 have been re-mapped to time points relative to the inception of the previous controlled studies.

LABORATORY EVALUATIONS

For hematology and clinical chemistry parameters, mean changes from baseline in the Phase 3 studies were small in magnitude and similar among treatment/dose groups.

VITAL SIGNS

Mean changes from baseline in systolic and diastolic blood pressures, pulse and respiration rates, and body temperature in the Phase 3 studies were small in magnitude and similar among treatment/dose groups.

BODY WEIGHT AND BODY MASS INDEX

At baseline, all treatment groups in the Phase 3 controlled studies had similar mean BMIs ranging from 27.74 to 28.25 kg/m². In both sodium oxybate treatment groups there was a decrease from baseline in mean body weight while in the placebo treatment group there was an increase from baseline in mean body weight. The magnitude of decrease in body weight was greater for the 6 g than the 4.5 g sodium oxybate group. Mean values for body weight in the Phase 3 placebo-controlled studies are displayed in Table 40.

Table 40. Summary Statistics of Body Weight (kg), Phase 3 Placebo-Controlled Studies

Visit	Placebo	SXB 4.5 g	SXB 6 g	All SXB
Baseline				
N	369	376	370	746
Mean (SD)	76.26 (15.217)	75.54 (14.810)	77.14 (14.804)	76.33 (14.819)
Median	74.20	74.60	76.45	75.30
Minimum, maximum	41.6, 121.3	46.9, 122.9	43.1, 123.4	43.1, 123.4
Week 4, Change from Baseline				
N	273	291	277	568
Mean (SE)	0.34 (0.093)	-0.10 (0.108)	-0.50 (0.116)	-0.29 (0.080)
Median	0.20	0.00	-0.40	-0.10
Minimum, maximum	-4.0, 7.5	-6.0, 9.6	-6.3, 10.0	-6.3, 10.0
Week 8, Change from Baseline				
N	252	262	240	502
Mean (SE)	0.50 (0.133)	-0.44 (0.143)	-0.95 (0.156)	-0.68 (0.106)
Median	0.40	-0.40	-0.60	-0.50
Minimum, maximum	-8.9, 8.1	-7.0, 7.8	-7.6, 8.9	-7.6, 8.9
Week 12, Change from Baseline				
N	244	249	218	467
Mean (SE)	0.51 (0.163)	-0.56 (0.180)	-1.54 (0.213)	-1.02 (0.140)
Median	0.50	-0.30	-1.05	-0.60
Minimum, maximum	-7.5, 13.2	-8.6, 9.1	-12.7, 7.1	-12.7, 9.1
Week 14/Early Term, Change from Baseline				
N	343	353	341	694
Mean (SE)	0.32 (0.122)	-0.75 (0.152)	-1.33 (0.168)	-1.04 (0.114)
Median	0.10	-0.30	-0.70	-0.40
Minimum, maximum	-8.4, 8.1	-10.0, 9.6	-12.7, 8.1	-12.7, 9.6

SD=standard deviation, SE=standard error, SXB=sodium oxybate

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Table 40. Summary Statistics of Body Weight (kg), Phase 3 Placebo-Controlled Studies

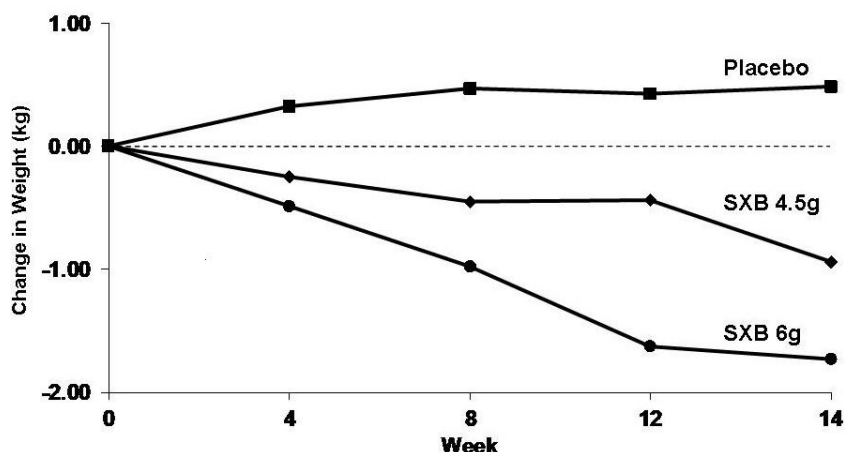
Visit	Placebo	SXB 4.5 g	SXB 6 g	All SXB
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Note: This table includes data from Studies 06-008 and 06-009. Baseline was the last value collected in the baseline period.
Source: ISS 4-month update Table 5.1.1.1

Figure 15 shows mean changes in body weight by treatment group in the Phase 3 placebo-controlled studies.

Note: Whereas the tables (except for [Table 41](#)) in this section show weeks assigned by the site, Figures 15 and 16 show weeks assigned based on actual number of days from randomization.

Figure 15. Change in Mean Body Weight Over Time, Phase 3 Placebo-Controlled Studies



* Week calculated based on number of days from randomization

[Figure 16](#) illustrates changes in body weight in the Phase 3 placebo-controlled studies as a frequency distribution of the number of subjects with various percentage categories of weight change by treatment group. The numbers of these subjects in each dose group experiencing a weight change of greater than 10% at week 14 are shown in [Table 41](#).

Figure 16. Number of Subjects by Percentage Weight Change at Week 14, Phase 3 Placebo-Controlled Studies

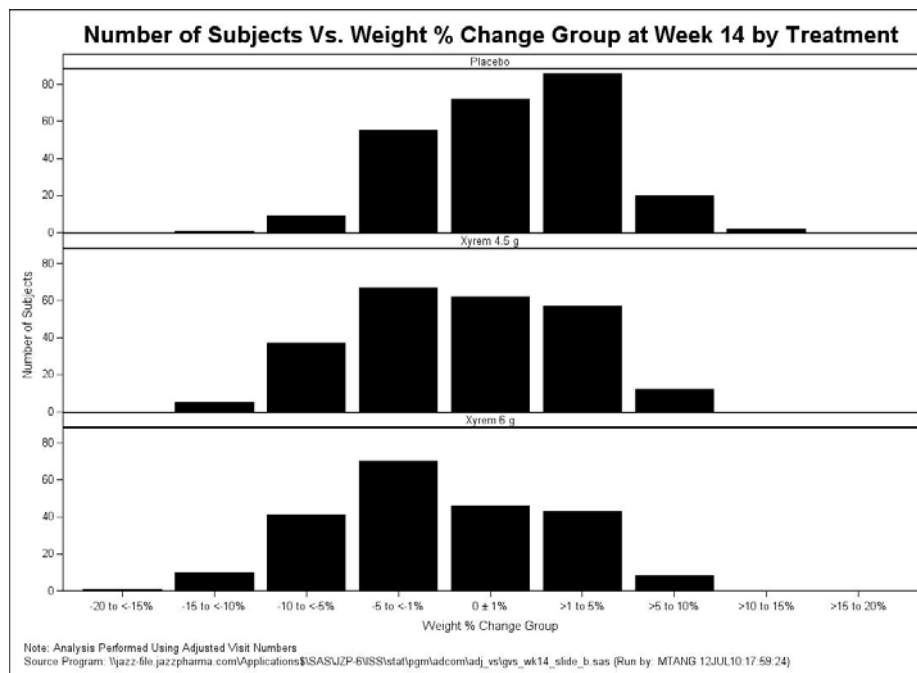


Table 41 Subjects with Weight Loss >10% or ≤10% in the Phase 3 Placebo-Controlled Studies

% Weight Loss at Week 14*	Placebo n=245	SXB 4.5g n=240	SXB 6g n=219
≤10%	90 (36.7)	132 (55.0)	135 (61.6)
>10%	1 (0.4)	5 (2.1)	11 (5.0)

* Week calculated based on number of days from randomization

Subjects who had underweight BMI at baseline and early termination in the Phase 3 placebo-controlled studies are summarized in Table 42. No subject in a sodium oxybate treatment group had a BMI of severe thinness (<16 kg/m²) at baseline or Week 14/Early Termination in the Phase 3 placebo-controlled studies. One subject who was randomized to Placebo had a BMI of 15.4 at baseline and at Week 14/early termination.

Table 42. Subjects with Underweight BMI (16 to <18.5kg/m²) at Baseline and Week 14/Early Termination, Phase 3 Placebo-Controlled Studies

Timepoint	Placebo	SXB 4.5 g	SXB 6 g	All SXB
Baseline	n=369 2 (0.5)	n=376 3 (0.8)	n=370 3 (0.8)	n=746 6 (0.8)
Week 14 or Early Discontinuation	n=344 4 (1.2)	n=353 4 (1.1)	n=342 6 (1.7)	n=695 10 (1.4)

BMI=body mass index, SXB=sodium oxybate

Mean weight changes over time in the cohort of subjects who participated in controlled studies 06-008 or 06-009 and in the open-label extension study 06-010 are displayed in Table 43 for those subjects who were randomized to sodium oxybate treatment groups in the controlled studies. Dosing for all subjects was initiated at 4.5 g in the open-label trial regardless of their randomized dose group in the prior controlled trial.

Table 43. Mean Changes from Baseline in Body Weight (kg) Over Time, Phase 3 Studies: Subjects Who Were Randomized to Sodium Oxybate Treatment Groups in Studies 06-008 and 06-009

Changes from Baseline by Time Point	N	Mean (SE)	Median	Minimum, Maximum
Baseline Values ^a	746	76.33 (14.819) ^b	75.30	43.1, 123.4
Week 4	568	-0.29 (0.080)	-0.10	-6.3, 10.0
Week 8	502	-0.68 (0.106)	-0.50	-7.6, 8.9
Week 12	467	-1.02 (0.140)	-0.60	-12.7, 9.1
Week 14/early termination	694	-1.04 (0.114)	-0.40	-12.7, 9.6
Day 1 of 06-010 ^c	40	-0.84 (0.486)	-0.35	-11.3, 4.7
Week 16	369	-1.32 (0.187)	-1.10	-15.9, 12.1
Week 18	352	-1.56 (0.208)	-0.90	-18.1, 12.3
Week 22	336	-2.03 (0.253)	-1.30	-28.1, 11.3
Week 26	305	-2.61 (0.274)	-1.40	-19.1, 12.0
Week 30	283	-2.96 (0.333)	-2.10	-28.5, 11.0
Week 34	268	-3.23 (0.355)	-2.30	-27.7, 9.8
Week 38	246	-3.68 (0.400)	-2.50	-29.0, 10.0
Week 42	221	-4.15 (0.439)	-2.70	-29.5, 8.7
Week 46	202	-4.58 (0.498)	-3.30	-29.5, 9.7
Week 50	180	-4.09 (0.546)	-2.90	-25.4, 28.4
Week 52	165	-4.81 (0.545)	-3.40	-26.3, 13.6
Endpoint ^d	716	-1.99 (0.192)	-0.80	-26.5, 28.4
Safety follow up	239	-3.67 (0.441)	-1.90	-27.2, 13.5

SE=standard error

Note: Data cutoff includes subject data from 06-010 through 02 September 2009 (database version, 15 December 2009) and incorporated errata from 06-008 and 06-009 (including adverse events first reported in 06-010 that had start dates in the prior studies).

^a Baseline was the last value collected during the baseline period of 06-008 or 06-009.

^b Values for baseline are mean (standard deviation)

^c The Day 1 visit of the 06-010 open-label study was optional based on the length of time between completion of 06-008/06-009 and beginning 06-010.

^d Endpoint was the last value collected during 06-008, 06-009, or 06-010 before the safety follow-up visit.

Source: ISS 4-month update Table 5.1.2.1

Adverse events relating to weight loss are summarized in the portion of [Section 4.4.1.5](#) addressing weight loss.

ELECTROCARDIOGRAMS

There were no notable electrocardiographic findings in any treatment/dose group in the Phase 3 studies.

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4.4.1.5 Safety Topics of Special Interest

SUICIDALITY

In the Phase 3 studies, a review of adverse event verbatim terms, tables and listings coded by MedDRA preferred terms, and subject diary data identified no terms consistent with adverse events related to suicidal ideation or behavior. No events meeting these criteria were identified in Phase 3 trials, including the open-label extension study.

In the Phase 2 study OMC-SXB-26, one event that included suicidal ideation was identified.

- A 53-year-old female experienced depression with suicidal thoughts on Day 15 of the study after approximately 14 nights of treatment with Sodium Oxybate 6 g/night. This event resolved approximately 1 week later, was not considered to be a serious adverse event, but was considered to be of severe intensity, possibly related to study drug, possibly related to the subject's clinical condition, and led to study discontinuation. The subject's medical history included allergy to mold, seasonal allergies, osteoarthritis, postmenopausal, asthma, chronic obstructive pulmonary disease, and fibromyalgia.

In addition to review of adverse event terms, a more conservative method for identifying potential suicide risk was employed. The MINI was used at all visits as a diagnostic tool to assess participants for the presence of suicidality and Major Depression. The BDI-II questionnaire was also used at every visit to measure the presence and degree of depressive symptoms and also includes a question that addresses the presence of suicidal thoughts or wishes (question 9) to assess suicidality risk.

This method identified 6 cases in Phase 3 trials in which subjects endorsed multiple items on these instruments and 30 cases in which subjects endorsed a single item indicating either a past history of suicidal behavior or current low level of potential suicide risk ("I have thoughts of killing myself, but I would not carry them out."). The 6 cases with multiple items endorsed are described below.

Placebo

- A 51-year-old male subject, randomized to Placebo in Study 06-008, had a low risk of suicidality at Week 8 based on positive endorsements on the MINI suicidality module and the BDI-II. During the remainder of the study no further positive endorsements were made. The subject did not report a history of depression. The subject completed Study 06-008 and did not continue in the open-label study.
- A 43-year-old female subject, randomized to Placebo in Study 06-009, endorsed positive responses for suicidality at Week 4, 8, 12, and 14 on the BDI-II but did not endorse current suicide risk on the MINI suicidality module. The subject met criteria on Day 1 for major depressive episode (MDE) on the MINI MDE module but was not current for MDE for the remainder of study. The subject met criteria for severe depression based on the BDI-II total scores (range 19 - 46) at baseline and throughout the study. The subject completed the study but did not enroll in the open-label study. The subject reported an 8-year history of depression at study entry.

Sodium Oxybate 4.5 g

- A 34-year-old female subject, who was receiving Sodium Oxybate 4.5 g nightly in both Study 06-009 and Study 06-010, experienced acute depression reported as an adverse

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event of moderate intensity on Day 259 (Month 9) of Study 06-010 that was considered not related to study drug. At Month 9 based on the BDI-II and the MINI suicidality module the subject had current and moderate risk for suicidality but without a plan or attempt. The subject also met criteria for a major depressive episode based on the MINI at Month 9. The subject was discontinued due to the event of acute depression on Day 259, the same day that the event occurred. The event resolved in 2 weeks. The subject did not report a history of depression at study entry.

Sodium Oxybate 6 g

- A 41-year-old female subject randomized to Sodium Oxybate 6 g nightly in Study 06-009, experienced depressed mood that was reported as an adverse event of moderate intensity that started 11 days prior to the first dose of study drug. The subject also had ‘bouts of crying as part of depressed mood’ reported as an adverse event that started on Day 1. Neither event was considered related to study drug. The subject endorsed low risk of suicidality on the BDI-II and the MINI met criteria for MDE. The subject was discontinued from study at Week 2 due to the event of depressed mood. The subject’s medical history is significant for depression treated with escitalopram, which was discontinued 3 days before the event of depressed mood began.
- A 45-year-old female subject randomized to Sodium Oxybate 6 g nightly experienced an adverse event of increased depression of moderate intensity on Day 88 (Week 12) of Study 06-009 that was considered related to study drug. The subject had concurrent events of abdominal pain, hernia pain, and worsening fibromyalgia and osteoarthritis. At Week 12 the subject endorsed a low risk of suicidality based on the BDI-II and the MINI, met criteria for MDE, and had a total score of 43 on the BDI-II, indicating severe depression. The events of increased depression and worsening of fibromyalgia led to study discontinuation on the same day that the event of increased depression began. The subject did not report a history of depression at study entry; however she did have a BDI-II total score of 31, indicating severe depression at baseline.
- A 41-year-old female subject who was receiving Sodium Oxybate 6 g nightly in both Study 06-009 and Study 06-010 had positively endorsed the question regarding suicidality on the BDI-II on Day 29 and Day 49 of Study 06-010. The subject did not meet criteria for suicidality on the MINI suicidality module during the study. On Day 49 the subject was discontinued from the study due an adverse event of rheumatoid arthritis that began in the previous study. The subject did not report any history of depression or suicidal ideation at entry into either study.

In an ongoing clinical trial in another program, one additional serious adverse event of suicide attempt was identified and is being reviewed.

From postmarketing experience with Xyrem, there were six completed suicides: From postmarketing experience with Xyrem, there were six completed suicides: the reporting physicians stated that one was possibly related to Xyrem and two were considered not related to Xyrem. In three cases, no relationship information was available.

In addition nonfatal reports of events related to suicidality from the Xyrem postmarketing experience are summarized in Table 44.

Table 44. Post-Marketing Reports of Suicides, Suicide Attempts and Events Potentially Related to Suicidal Ideation (07 July 2002 to 01 May 2010)

Preferred Term	Number of reports	Cases per 100 Patient-Years of Exposure
Completed Suicide	6	0.02
Suicide Attempts	16	0.05
Suicidal Ideation	63	0.20

Subsequent to this analysis, one additional suicide attempt event was identified in the postmarketing experience for Xyrem; the case is being reviewed.

DEPRESSION

In the Phase 3 studies, subjects were excluded for a current diagnosis or current treatment of major depressive disorder. To avoid confounding the assessment of response to sodium oxybate treatment for fibromyalgia, subjects entering the Phase 3 studies were required to withdraw from antidepressant therapy; any subject who could not or was at increased risk of harm from doing this was excluded from participation. Depression was assessed from data provided on the MINI major depressive episode module and the BDI-II questionnaire.

Treatment-emergent depression-related adverse events from the Phase 2 and 3 placebo-controlled studies are summarized in Table 45.

Table 45. Treatment-Emergent Depression-Related Adverse Events, Phase 2 and 3 Controlled Trials

Number (%) of Subjects with	Placebo (n=436)	SXB 4.5 g (n=436)	SXB 6 g (n=438)	All SXB (n=874)
Depression/depressed mood ^a	6 (1.4)	10 (2.3)	14 (3.2)	24 (2.7)
Discontinued due to depression/depressed mood ^a	4 (0.9)	1 (0.2)	6 (1.4)	7 (0.8)
Major depression	2 (0.5)	2 (0.5)	1 (0.2)	3 (0.3)
Discontinued due to major depression	0	0	0	0

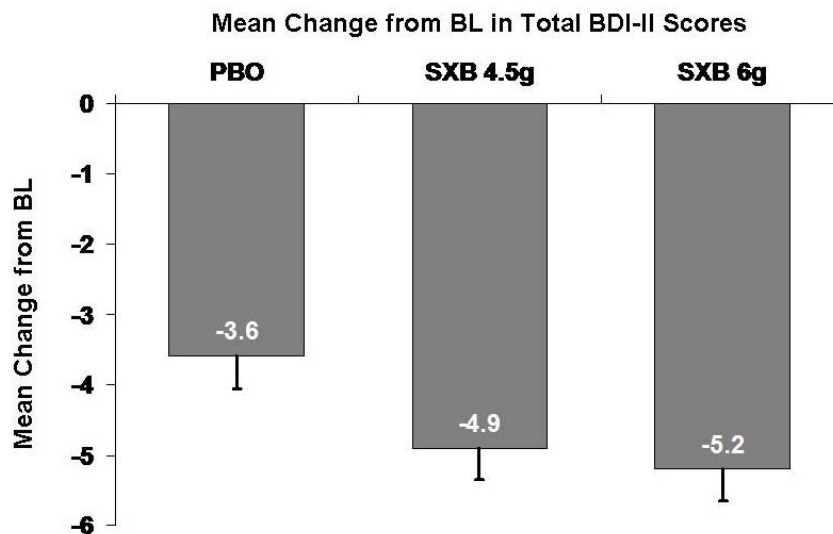
SXB=sodium oxybate

^a Terms were assessed as representing a common clinical phenomenon; the numbers of subjects have been combined for these terms.

Source: ISS 4-month database

Figure 17 shows the mean change from baseline in the BDI-II total scores by treatment group at Week 14 in the Phase 3 placebo-controlled studies. A decreasing total score on the BDI-II indicates decreasing depressive symptoms.

Figure 17. Mean Change from Baseline in BDI-II Total Score at Week 14, Phase 3 Placebo-Controlled Studies



BL=baseline, PBO=placebo, SXB=sodium oxybate
Source: ISS 4-month update Table 6.1.1

In the clinical studies in subjects with fibromyalgia, no depression-related adverse event was considered to be a serious adverse event.

Treatment-emergent depression-related adverse events that occurred in the Phase 3 open-label study are summarized in Table 46.

Table 46. Treatment-Emergent Depression-Related Adverse Events, Phase 3 Open-Label Study (06-010)

Number (%) of Subjects with	SXB 4.5 g (N=545)	SXB 6 g (N=431)	SXB 7.5 g (N=238)	SXB 9 g (N=112)	All SXB (N=560)
Depression/depressed mood ^a	9 (1.7)	10 (2.3)	5 (2.1)	2 (1.8)	24 (4.6)
Discontinued due to depression/depressed mood ^a	5 (0.9)	2 (0.5)	2 (0.8)	1 (0.9)	10 (1.8)
Major depression	1 (0.2)	0	1 (0.4)	1 (0.9)	3 (0.5)
Discontinued due to major depression	0	0	0	0	0

SXB=sodium oxybate

^a Terms were assessed as representing a common clinical phenomenon; the numbers of subjects have been combined for these terms.

Reports of events related to depression from the Xyrem postmarketing experience are summarized in Table 47.

Table 47. Postmarketing Reports of Events Related to Depression (07 July 2002 to 01 May 2010)

Preferred Terms	Number of Events Reported	Cases per 100 Patient-Years of Exposure
Depression	369	1.17
Depressed mood	46	0.15
Depressive symptom	7	0.02
Major depression	2	0.01

CNS DEPRESSION

Among the most common ($\geq 2\%$) adverse events reported in the Phase 2 and Phase 3 studies, somnolence occurred in 12 (3.2%) subjects each in the placebo and 4.5 g groups, 19 (5.1%) subjects in the 6 g group, and 31 (4.1%) subjects in the All Sodium Oxybate group.

Treatment-emergent adverse events considered potential outcomes resulting from CNS depression in the Phase 2 and Phase 3 controlled studies are summarized in Table 48. Based on clinical review, one event was of clinical relevance. One patient experienced depressed level of consciousness (verbatim term: loss of alertness) of moderate intensity at a dose of 6 g sodium oxybate. The event was considered related to study drug, and the subject was discontinued from the study for this adverse event.

Table 48. Treatment-Emergent Adverse Events Considered Outcomes Potentially Related to CNS Depression, Phase 2 and 3 Placebo-Controlled Trials

Number (%) of Subjects with	Placebo (N=436)	SXB 4.5 g (N=436)	SXB 6 g (N=438)	All SXB (N=874)
Fall	3 (0.7)	2 (0.5)	3 (0.7)	5 (0.6)
Road traffic accident	1 (0.2)	3 (0.7)	1 (0.2)	4 (0.5)
Depressed level of consciousness	0	0	1 (0.2)	1 (0.1)
Unresponsive to stimuli ^a	0	0	1 (0.2)	1 (0.1)

SXB=sodium oxybate

^a Verbatim term: unresponsiveness

Source: ISS 4-month update Table 4.5.3.1

Treatment-emergent adverse events considered to be potential outcomes resulting from CNS depression in the Phase 3 open-label study are summarized in [Table 49](#).

Based on clinical review, one event was of clinical relevance: One patient experienced an adverse event of loss of consciousness (verbatim term loss of consciousness; hard to arouse) of severe intensity at a dose of 7.5 g sodium oxybate. The event was considered related to study drug, and the subject was discontinued from the study for an adverse event of vomiting. The event resolved the next day.

Table 49. Treatment-Emergent Adverse Events Considered Outcomes Potentially Related to CNS Depression, Phase 3 Open-Label Trial (06-010)

Number (%) of Subjects with	SXB 4.5 g (N=545)	SXB 6 g (N=431)	SXB 7.5 g (N=238)	SXB 9 g (N=112)	All SXB (n=560)
Fall	8 (1.5)	5 (1.2)	2 (0.8)	3 (2.7)	16 (2.9)
Road traffic accident	1 (0.2)	2 (0.5)	0	0	3 (0.5)
Accident	1 (0.2)	1 (0.2)	0	0	2 (0.4)
Depressed level of consciousness	0	1 (0.2)	0	1 (0.9)	2 (0.4)
Loss of consciousness	0	0	1 (0.4)	0	1 (0.2)

SXB=sodium oxybate

Source: ISS 4-month database

Reports of events considered to be potential outcomes resulting from CNS depression from the Xyrem postmarketing experience are summarized in Table 50. None of the events was fatal.

Table 50. Postmarketing Reports of Events Potentially Related to CNS Depression (07 July 2002 to 01 May 2010)

Preferred Terms	Number of Events Reported	Cases per 100 Subject-Years of Exposure
Depressed level of consciousness	8	0.03
Loss of consciousness ^a	27	0.09
Unresponsive ^a	1	<0.01

^a Includes 15 cases of transient loss of consciousness that resolved without medical intervention.

^b Verbatim term: became unresponsive

RESPIRATORY DEPRESSION

Treatment-emergent adverse events potentially related to respiratory depression in the Phase 2 and 3 placebo-controlled studies are summarized in Table 51.

Table 51. Treatment-Emergent Adverse Events Potentially Related to Respiratory Depression, Phase 2 and 3 Placebo-Controlled Studies

Number (%) of Subjects with	Placebo (N=436)	SXB 4.5 g (N=436)	SXB 6 g (N=438)	All SXB (N=874)
Apnea	0	0	1 (0.2)	1 (0.1)
Respiratory rate decreased	0	0	1 (0.2)	1 (0.1)
Hypoventilation	0	1 (0.2)	0	1 (0.1)

Note: Preferred terms selected based on manual review of the adverse event summary table. Adverse events are summarized by randomized treatment.

Source: ISS 4-month Table 4.5.3.1

Treatment-emergent adverse events potentially related to respiratory depression in the Phase 3 open-label study (06-010) are summarized in Table 52.

Table 52. Treatment-Emergent Adverse Events Potentially Related to Respiratory Depression, Phase 3 Open-Label Trial (06-010)

Number (%) of Subjects with	SXB 4.5 g (N=545)	SXB 6 g (N=431)	SXB 7.5 g (N=238)	SXB 9 g (N=112)	All SXB (n=560)
Respiratory depression	0	0	0	1 (0.9)	1 (0.2)
Respiratory rate decreased	0	1 (0.2)	0	0	1 (0.2)
Apnea	1 (0.2)	1 (0.2)	0	0	2 (0.4)

SXB=sodium oxybate
Source: ISS 4-month database

Events potentially related to respiratory depression from the postmarketing experience with Xyrem are summarized in Table 53. None of these events was fatal.

Table 53 Post-Marketing Reports of Events Potentially Related to Respiratory Depression (07 July 2002 to 01 May 2010)

Preferred Terms	Number of Reports	Cases per 100 Patient-Years of Exposure
Hypoventilation	1	0.01
Hypoxia	3	0.01
Respiratory Arrest	9	0.03
Respiratory Depression	6	0.02
Respiratory Failure	2	0.01
Respiratory Distress	2	0.01
Respiratory Rate Decreased	1	<0.01

SLEEP DISORDERS

Adverse events related to sleep disorders in the Phase 2 and 3 placebo-controlled studies are summarized in Table 54.

Table 54. Treatment-Emergent Adverse Events Potentially Related to Sleep Disorders, Phase 2 and 3 Placebo-Controlled Trials

Number (%) of Subjects with	Placebo (N=436)	SXB 4.5 g (N=436)	SXB 6 g (N=438)	All SXB (N=874)
Sleep walking	0	3 (0.7)	1 (0.2)	4 (0.5)
Sleep paralysis	0	0	3 (0.7)	3 (0.3)
Sleep talking	0	0	1 (0.2)	1 (0.1)
Parasomnia	0	1 (0.2)	0	1 (0.1)
Sleep apnea syndrome	1 (0.2)	0	0	0

SXB=sodium oxybate
Source: ISS 4-month Table 4.5.3.1

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Adverse events related to sleep disorders in the Phase 3 open-label study (06-010), are summarized in Table 55.

Table 55. Treatment-Emergent Adverse Events Potentially Related to Sleep Disorders, Phase 3 Open-Label Trial (06-010)

Number (%) of Subjects with	SXB 4.5 g (N=545)	SXB 6 g (N=431)	SXB 7.5 g (N=238)	SXB 9 g (N=112)	All SXB (n=560)
Sleep walking	0	2 (0.5)	2 (0.8)	1 (0.9)	5 (0.9)
Sleep paralysis	2 (0.4)	2 (0.5)	0	0	4 (0.7)
Sleep talking	0	0	1 (0.4)	0	1 (0.2)
Parasomnia	0	1 (0.2)	0	0	1 (0.2)
Hypersomnia	1 (0.2)	0	0	1 (0.9)	2 (0.4)
Sleep apnea syndrome	0	1 (0.2)	0	0	1 (0.2)

SXB=sodium oxybate

Source: ISS 4-month database

Reports of events potentially related to sleep disorders from the Xyrem postmarketing experience are summarized in Table 56.

Table 56. Postmarketing Reports of Events Potentially Related to Sleep Disorders (07 July 2002 to 01 May 2010)

Preferred Terms	Number of Events Reported	Cases per 100 Patient-Years of Exposure
Parasomnia	19	0.06
Sleep apnea syndrome ^b	68	0.21
Sleep terror	26	0.08
Sleep walking ^c	258	0.82
Sleep talking	44	0.14
Sleep paralysis	70	0.22
Sleep eating	19	0.06

^a Includes, insomnia, initial insomnia, middle insomnia, terminal insomnia, irregular sleep phase, delayed sleep phase.

^b Includes upper airway resistance syndrome, breathing-related sleep disorder

^c Includes somnambulism

WEIGHT LOSS

In the Phase 2 and Phase 3 placebo-controlled studies, adverse events related to changes in body weight and changes in appetite are summarized in Table 57.

Table 57. Treatment-Emergent Adverse Events Related to Weight Loss, Phase 2 and 3 Placebo-Controlled Studies

Number (%) of Subjects with	Placebo (N=436)	SXB 4.5 g (N=436)	SXB 6 g (N=438)	All SXB (N=874)
Weight decreased	1 (0.2)	10 (2.3)	8 (1.8)	18 (2.1)
Anorexia	1 (0.2)	9 (2.1)	7 (1.6)	16 (1.8)
Decreased appetite	2 (0.5)	7 (1.6)	9 (2.1)	16 (1.8)
Bulimia nervosa	0	1 (0.2)	0	1 (0.1)

SXB=sodium oxybate

Note: Preferred terms selected based on manual review of the adverse event summary table. Adverse events are summarized by randomized treatment.

Source: ISS 4-month Table 4.5.3.1

In the Phase 3 open-label study, adverse events related to changes in body weight and changes in appetite are summarized in Table 58.

Table 58. Treatment-Emergent Adverse Events Related to Weight Loss, Phase 3 Open-Label Trial (06-010)

Number (%) of Subjects with	SXB 4.5 g (N=545)	SXB 6 g (N=431)	SXB 7.5 g (N=238)	SXB 9 g (N=112)	All SXB (n=560)
Weight decreased	6 (1.1)	10 (2.3)	3 (1.3)	2 (1.8)	21 (3.8)
Anorexia	2 (0.4)	8 (1.9)	4 (1.7)	2 (1.8)	16 (2.9)
Decreased appetite	7 (1.3)	4 (0.9)	3 (1.3)	0	13 (2.3)

SXB=sodium oxybate

Source: ISS 4-month database

HYPERTENSION AND EDEMA

For subjects in the Phase 2 and Phase 3 placebo-controlled fibromyalgia studies, the incidence of adverse events potentially related to hypertension and edema is summarized in [Table 59](#). Sodium oxybate placebo contained amounts of sodium identical to each of the active treatments in 06-008 and identical to the Sodium Oxybate 6 g active treatment in 06-009.

Table 59. Treatment-Emergent Adverse Events Potentially Related to Hypertension and Edema, Phase 2 and 3 Placebo-Controlled Studies

Number (%) of Subjects with	Placebo (N=436)	SXB 4.5 g (N=436)	SXB 6 g (N=438)	All SXB (N=874)
Blood pressure increased/ blood pressure diastolic increased/blood pressure systolic increased/hypertension ^a	6 (1.4)	8 (1.8)	18 (4.1)	26 (3.0)
Edema peripheral	8 (1.8)	6 (1.4)	17 (3.9)	23 (2.6)
Edema/generalized edema/swelling ^a	2 (0.5)	3 (0.7)	2 (0.5)	5 (0.6)
Fluid retention	0	1 (0.2)	3 (0.7)	4 (0.5)

SXB=sodium oxybate

^a Terms were assessed as representing a common clinical phenomenon; the numbers of subjects have been combined for these terms.

Note: Preferred terms selected based on manual review of the adverse event summary table. Adverse events are summarized by randomized treatment.

Source: ISS 4-month Table 4.5.3.1

CONVULSIONS/SEIZURES

The FDA, as part of routine monitoring, evaluates drug safety information in its AERS database to determine if there are any potential signals of serious risks/new safety information. In the most recent quarter, FDA identified a potential signal related to convulsions in the Xyrem data. FDA states that the appearance of a drug on this list does not mean that FDA has concluded that the drug has the listed risk. It means that FDA has identified a *potential safety issue*, but does not mean that FDA has identified a causal relationship between the drug and the listed risk. We have included the information from our post marketing database related to convulsions.

No adverse events related to seizures were reported in the Phase 2 and Phase 3 placebo-controlled studies or in the Phase 3 open-label study.

Events potentially related to convulsions or seizures from the postmarketing experience with Xyrem are summarized in Table 60.

Table 60 Post-Marketing Reports of Events Potentially Related to Convulsions/Seizures (07 July 2002 to 01 May 2010)

Preferred Terms	Number of Reports	Cases per 100 Patient-Years of Exposure
Convulsions/Seizures ^a	78	0.25

^a Includes 10 grand mal seizures and 1 partial/complex seizure

ANALYSIS OF SAFETY DATA IN SUBPOPULATIONS

Analyses of adverse events were performed for subgroups defined by age (<65 and ≥65 years), gender (male and female), race (Caucasian and non-Caucasian), BMI category (<30 and ≥30 kg/m²), dose/body weight ratio (0 to <60, 60 to 80, and >80 mg/kg), and BDI-II total score (≤13 and >13).

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In general, sample sizes were disproportionate, thus limiting the ability to draw meaningful conclusions. However, in Phase 2 and 3 trials, the proportion of subjects with any adverse event was higher for subjects ≥ 65 years of age and for subjects with a dose/body weight ratio >80 mg/kg, as follows:

- 92.9% in subjects ≥ 65 years of age versus 85.8% in subjects <65 years of age
- 83.6% in subjects with a dose/body weight ratio >80 mg/kg, compared with 68.9% and 70.3% in the 0 to <60 and 60 to 80 mg/kg groups, respectively.

In the Phase 3 studies, mean decreases in body weight were less for subjects ≥ 65 years of age, female subjects, and non-Caucasian subjects. Body weight decreases $\geq 15\%$ were observed more commonly in female and Caucasian subjects.

DATA RELEVANT TO ABUSE AND MISUSE

Dosing and Study Compliance

In the Phase 3 studies, subjects reported a high degree of compliance with the twice-nightly dosing regimen: Subjects reported taking two doses per night for $\geq 98.5\%$ of subject-nights of exposure in all dose groups.

Monitoring reports in 06-009 identified four cases in which subjects took 150% of the intended dose for some period of time during the study (three subjects receiving sodium oxybate and one subject receiving placebo). Two of the subjects reported no adverse events while taking 150% of the intended dose, one subject reported fever and dry cough considered unrelated to study drug, and one subject reported adverse events of gait disturbance and tremor—considered of moderate and mild intensity, respectively, and both considered related to treatment—that led to study discontinuation.

In the fibromyalgia clinical trials, four additional dosing deviations involved dosing at >9 g/night.

- One subject reported taking sodium oxybate 15 g/night on Days 29–41 of Study 06-010. The investigator discontinued this subject from the study for noncompliance with study drug dosing. The subject reported adverse events of nausea and feeling jittery (considered mild and moderate in severity, respectively; both related to treatment) and an upper respiratory tract infection (considered mild and unrelated to treatment) during the time period she was taking 15 g/night.
- One subject was hospitalized for encephalopathy due to an accidental overdose of sodium oxybate. The subject had received sodium oxybate at doses up to 9 g/night for 171 days in Study 06-010. On the night in question, she reported inadvertently taking 13.5 g. The course of these serious adverse events is described in [Section 4.4.1.3](#) (Deaths and Other Serious Adverse Events).
- One subject (receiving sodium oxybate 7.5 g in 06-010) reported taking three instead of two doses on a single night, for a total of 11.25 g.
- One subject (receiving sodium oxybate 9 g in 06-010) reported taking three instead of two doses on a single night, for a total of 13.5 g.

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The 06-010 study protocol required all subjects to begin sodium oxybate treatment in that study at the 4.5 g dose; five subjects began treatment at doses up to 9 g/night due to error, misunderstanding of the dosing instructions, or investigator decision.

One case of potential misuse was revealed during database edit checks in Study 06-008. Two subjects (both randomized to the Sodium Oxybate 6 g group), enrolled at different sites in Study 06-008 in the same vicinity and at different times, appear to have been the same individual, based on having the same initials and birthdate. The first subject enrolled in Study 06-008 on 19 January 2007, completed the study on 27 April 2007, and was subsequently enrolled in Study 06-010. The second subject was enrolled in Study 06-008 on 20 August 2007 and withdrew consent 12 days later, saying that she could no longer attend the required clinic visits. She was dispensed drug for the first week of treatment but never returned to the clinic or returned the drug supplies dispensed. Misuse is suspected in this case, but based on the volumes dispensed and returned at both sites, there was no clear evidence of diversion. No adverse events related to potential abuse were noted in this subject, and there was no conclusive evidence of abuse.

Adverse Events from Fibromyalgia Clinical Trials

Other than those adverse events described in the previous section, there were no adverse events indicative of abuse, dependence, misuse, overdose, or severe withdrawal during study treatment for all treated subjects in the Phase 2 and 3 placebo controlled-studies, during the 2-week period after the final dose of study drug for those subjects who did not participate in study 06-010, or during the 2-week period after the final dose of study drug as of the cutoff for inclusion in the 4-month safety update ISS.

Xyrem Postmarketing Data

From the Xyrem postmarketing experience, there were four deaths involving overdose. In one case the physician stated that the death was related to Oxycontin overdose. In two cases, the physicians stated that the deaths were not related to Xyrem. In one case, the physician reported that the patient was on multiple sleep medications; no information about relationship to Xyrem was reported. Nonfatal reports of events possibly related to abuse, misuse, overdose, or dependence are summarized in Table 61.

Table 61. Postmarketing Reports of Events Potentially Related to Overdose/Misuse/Dependence (07 July 2002 to 01 May 2010)

Preferred Terms	Number of Events Reported	Cases per 100 Patient-Years of Exposure
Multiple drug overdose intentional	2	0.01
Overdose	6	0.02
Drug abuse	4	0.01
Drug dependence	4	0.01
Intentional overdose	2	0.01
Multiple drug overdose	9	0.02

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4.4.2 Adverse Event Profile with Use of Sodium Oxybate in the Narcolepsy Patient Population

The ISS for the narcolepsy indication, last updated in January 2006, includes a total of 781 patients in 10 integrated clinical efficacy and safety studies. The mean duration of Xyrem treatment was 518 days, with 42.8% of patients being treated for at least one year. The mean age of the patients exposed to Xyrem was 43.4 years and 59% were female. The mean age of 132 patients treated with placebo (only) was 39.7 years and 56% were female.

Adverse events were reported for 60.0% of patients receiving placebo, and 86.3% treated with Xyrem; the proportions of patients with adverse events at 3, 4.5, 6, 7.5 and 9 g/night were 61.3%, 51.0%, 61.5%, 65.7% and 72.2%, respectively. Treatment-related adverse events (defined as having a possible or closer relationship to treatment) were reported for 31.9% of placebo-treated patients and 64.9% of Xyrem-treated patients. Treatment-related adverse events were reported for 39.6%, 33.5%, 39.1%, 35.3% and 51.5% of patients treated at 3, 4.5, 6, 7.5, and 9 g/night, respectively.

Five deaths occurred in the narcolepsy clinical trials: two from drug overdose, two from cancer, and one with chest pain. The two deaths from overdose resulted from ingestion of multiple drugs, including sodium oxybate in one patient. The two cases of cancer included one patient with metastatic endometrial carcinoma secondary to liver cancer, and one patient with lung cancer. The fifth case was a patient with chest pain. None of the deaths was considered related to Xyrem treatment by the investigator.

Serious adverse events were reported for 79 patients (10.1%) treated with Xyrem, including the five deaths described in the previous paragraph, and five (1.9%) treated with placebo in the 10 integrated clinical studies; the serious adverse events were described as treatment related in 20 patients (2.6%) and one patient (0.4%), respectively. In total, 115 Xyrem-treated patients (14.7%) and five placebo-treated patients (1.9%) discontinued treatment because of adverse events; 82 (10.5%) and three (1.2%) discontinued treatment because of treatment-related adverse events. The adverse events leading to discontinuation of treatment were generally those commonly seen during Xyrem treatment, such as nausea or events of the central nervous system.

The most common adverse events (MedDRA preferred terms) associated with Xyrem treatment were nausea (23.8% versus 3.5% on placebo) and headache (24.2% compared with 15.4% on placebo). Other adverse events that affected an appreciably higher proportion of Xyrem-treated patients than placebo-treated patients, all causalities and treatment-related, included abdominal pain upper, diarrhea, nausea, vomiting, asthenia, fatigue, feeling drunk, peripheral edema, fall, loss of appetite (includes the term anorexia), arthralgia, cataplexy, muscle cramp, myalgia, disturbance in attention, dizziness, headache, paresthesia, somnolence, tremor, abnormal dreams, anxiety, confusional state, depression, disorientation, nervousness, nightmare, sleep walking, enuresis, and hyperhidrosis. There was strongest evidence of a relationship between incidence and dose for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking and enuresis.

The adverse event profile in the updated narcolepsy ISS was in line with that previously reported. Many observed events were anticipated with use of a centrally acting compound in patients with narcolepsy.

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Study OMC-SXB-23 assessed the effects of sodium oxybate alone and with modafinil compared with placebo and the positive control zolpidem on the incidence of sleep-disordered breathing events and oxygenation in patients with OSAS. In this study, sodium oxybate, first administered at a dose of 9 g/night (as two 4.5 g doses) in a single night's exposure, did not increase the severity of sleep-disordered breathing and resulted in a statistically significant improvement in the apnea-hypopnea index relative to the positive control zolpidem. During 2 weeks of double-blind treatment at a dose of 4.5 g/night or placebo followed by one night of double-blind dosing at 9 g/night or placebo, sodium oxybate did not adversely affect the duration and severity of oxygen desaturation. Administration of sodium oxybate 4.5 g/night for 2 weeks resulted in improvement relative to placebo on the apnea-hypopnea index on the following night, indicating that more prolonged administration did not adversely affect respiratory control mechanisms. Based on results from OMC-SXB-23, the agency released the sponsor from a Phase 4 commitment to perform an additional study in subjects with OSAS.

In the narcolepsy clinical development program, the respiratory depressant effects of sodium oxybate, when administered at recommended doses, were assessed in 21 patients with narcolepsy, and no dose-related changes in oxygen saturation were demonstrated in the group as a whole. Four of these 21 subjects had moderate-to-severe sleep apnea. One of the four patients with sleep apnea had significant worsening of the apnea/hypopnea index during treatment, but worsening did not increase at higher doses. Another patient discontinued treatment because of a perceived increase in clinical apnea events. In the randomized controlled Trials 3 and 4 (OMC-SXB-15 and OMC-SXB-22, respectively), a total of 40 narcolepsy patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a worsening of their respiratory function as measured by apnea/hypopnea index and pulse oximetry while receiving sodium oxybate at dosages of 4.5 to 9 g/night in divided doses.

4.4.3 Safety Conclusions

In conclusion, the adverse event profile for sodium oxybate in the treatment of fibromyalgia was consistent with that observed in clinical trials with narcolepsy and with the Xyrem postmarketing safety data obtained through the existing risk management program.

Based on data from the clinical trials in fibromyalgia and the postmarketing experience with the marketed sodium oxybate product Xyrem, we have identified the risks with sodium oxybate treatment that should appropriately be mitigated through the product labeling, and others that should be addressed specifically by the REMS program.

4.4.3.1 Risks Identified for Mitigation through the REMS

The following paragraphs summarize those primary safety risks identified for mitigation through the REMS program, including through the proposed product labeling. In addition, other adverse events that represent potential safety risks to patients are conveyed in the proposed prescribing information for sodium oxybate for the treatment of fibromyalgia (see [Appendix A](#)). Because we have not completed the FDA review process, final language for the label has not been completed with FDA and we will work with them to finalize appropriate language for risk communication.

CNS- and Respiratory-Depressant Effects. The CNS-depressant effects of sodium oxybate have the potential to cause respiratory depression and decreases in the level of consciousness, including rare instances of coma and death, as noted in the boxed warning of the proposed product label. The proposed risk mitigation for this risk focuses on the education of prescribers and patients to make them aware of the risks for CNS and respiratory depression and provide important information about the safe use of the product, including the need to appropriately evaluate patients with compromised respiratory function who are prescribed sodium oxybate.

The proposed label also carries a boxed warning about the CNS-depressant effects of sodium oxybate and warns against the use of sodium oxybate with alcohol or CNS depressants.

Abuse. The proposed label has a boxed warning noting that GHB is a known drug of abuse and that abuse of GHB has been associated with important CNS adverse events. In addition to the established controls against diversion, abuse, and misuse that are inherent in sodium oxybate's status as a Schedule III controlled substance, the proposed REMS program summarized in [Section 5](#) has a tightly controlled, proven prescription and distribution process that includes checks to prevent a patient from being prescribed more than one sodium oxybate-containing product at a time and to monitor for potential abuse or misuse. The proposed label and Medication Guide instruct physicians, pharmacists, and patients about the safe use, handling, and disposal of the product; describe the risks of abuse; and state clearly that patients should not give or sell their medication to anyone else.

The proposed REMS for sodium oxybate for fibromyalgia, paralleling the current REMS for Xyrem, is designed to clearly and effectively communicate the risks of this medication to patients, pharmacists, physicians, and caregivers, while ensuring its availability to the appropriate patient population.

5 RISK EVALUATION AND MITIGATION STRATEGY

The risks of sodium oxybate include risks to the individual patient as well as societal risks. The current risk evaluation and mitigation strategy (REMS) program for the marketed product, Xyrem, has been functioning for nearly 8 years to mitigate both risks to the individual patient and societal risks.

Individual patient risks are mitigated through prescriber and patient education, documentation of safe use conditions for patients, and clear warnings about sodium oxybate's CNS- and respiratory-depressant effects and the potential for suicidality and depression in the physician labeling and the patient Medication Guide. The REMS is an active system with multiple direct conversations with patients that provide opportunities for patients to ask questions and seek advice about the information they are given.

Programs and initiatives over the years have significantly reduced illicit GHB use. However, a low level of abuse of illicit GHB continues to exist. The FDA, in its efforts to create a single REMS program for all extended-release opioid products, recently concluded that societal problems surrounding the illicit use of drugs cannot be addressed with a REMS program. However, any additional societal risks of abuse, misuse, sexual assault, and diversion created by the new indication of sodium oxybate to treat fibromyalgia will be mitigated through a well-controlled, interactive distribution system, prescriber and patient enrollment in the REMS program, monitoring of early refill requests and other instances of potential abuse, and strong warnings about the risks of abuse and misuse. These actions augment the restrictions that derive from sodium oxybate's status as a Schedule III controlled substance. Although no REMS program can prevent all risk, the Xyrem REMS has been effective in mitigating both the individual and societal risks associated with this product. The proposed REMS for the new fibromyalgia indication has the same proven design as the existing program, which augurs well for its success.

5.1 Goal of the Proposed REMS for Sodium Oxybate

The goal of the overall sodium oxybate REMS is to ensure proper communication of the risk information for sodium oxybate for fibromyalgia and for the commercial product Xyrem, including the risks of CNS events when any sodium oxybate product is used alone or in combination with ethanol (alcohol) or other CNS-depressants, and to mitigate the potential abuse and misuse of the products.

The proposed REMS for sodium oxybate includes both the sodium oxybate product for the treatment of fibromyalgia and the current commercial product Xyrem[®] (sodium oxybate) oral solution, which has approved indications for treatment of excessive daytime sleepiness (EDS) and cataplexy in narcolepsy. This goal is achieved through the following:

- Appropriate labeling for prescribers and patients
- An enrollment program to facilitate active communication for patients about the information they receive, as well as cross-checking for duplicate sodium oxybate use
- A distribution system that ships from a limited number of specialty certified pharmacies directly to patient homes, thus constraining the supply of product that could be available for diversion through such activities as prescription shopping and providing feedback on potential abuse, misuse, or diversion.

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The two sodium oxybate products will have parallel but distinct distribution processes; the distribution of sodium oxybate for fibromyalgia will incorporate controls similar to those effectively used in the current risk management program for Xyrem. A Central Processing Function (CPF) and Data Coordination Center (DCC) will enable certified pharmacies to ensure that no patient receives both products and to monitor for prescription abuse or misuse. No retail pharmacy will dispense either sodium oxybate product. We anticipate certifying approximately 15 specialty pharmacies initially. **No certified pharmacy will dispense both sodium oxybate for fibromyalgia and Xyrem.**

Please note that this briefing document section focuses on the REMS elements for sodium oxybate for fibromyalgia, the subject of this application.

5.2 Risks Described and Mitigated in the Labeling

The primary risk mitigation is to ensure that prescribers, pharmacists, patients, and caregivers are made aware of the risks associated with the product, which will allow prescribers to make an informed decision in determining whether sodium oxybate therapy is appropriate for a given patient. The prescribing information for prescribers and the Medication Guide for patients provide the information on the contraindications, warnings, and precautions to consider in using this product. The final labeling will be the product of further review and input by FDA.

As with any drug treatment, there are risks associated with sodium oxybate treatment, some of which derive from properties related to its effectiveness. In clinical use of sodium oxybate in patients with fibromyalgia or narcolepsy, the associated risks have been safely managed by appropriate dosing and administration; prescriber and patient education about the risks of CNS and respiratory depression, with or without concomitant use of alcohol or other CNS depressants; clear language in the proposed product label about contraindications and use in specific populations (eg, patients with compromised respiratory function, hepatic insufficiency, or conditions sensitive to sodium intake); and appropriate warnings and precautions about suicidality and abuse potential.

Clinical trial data and nearly 8 years of postmarketing experience in approximately 35,000 US patients using Xyrem provide strong support for the safe use of sodium oxybate in both patient populations, document the low incidence of events of CNS and respiratory depression and abuse, and establish the effectiveness of the distribution program used to educate prescribers, patients, and pharmacists about how to safely use sodium oxybate.

5.2.1 CNS- and Respiratory-Depressant Effects

The CNS-depressant effects of sodium oxybate have the potential to cause respiratory depression and decreases in the level of consciousness, including rare instances of coma and death, as stated in the boxed warning. The proposed risk mitigation for this product focuses on the education of prescribers and patients to make them aware of the risks for respiratory depression and provide important information about the safe use of the product. The proposed label carries a boxed warning against the use of sodium oxybate with alcohol or CNS depressants. As with all drugs with central depressant effects, prescribers are informed about the need to appropriately evaluate patients with compromised respiratory function who are prescribed sodium oxybate. The proposed label also includes language informing

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prescribers that sleep-disordered breathing tends to be more prevalent in obese patients and in postmenopausal women not on hormone replacement therapy.

The proposed label also contains a warning about CNS depression with sodium oxybate. The impact of adverse CNS-depressant effects is potentially decreased by the nighttime dosing regimen. Due to sodium oxybate's short half-life, which limits the duration of exposure, the level of next-day impairment is relatively low. Nevertheless, we propose strong label warnings and education for both patients and prescribers about the product's potential for CNS-depressant effects. The proposed label for sodium oxybate for fibromyalgia includes a boxed warning noting the potential for CNS depression and states clearly that patients should not use sodium oxybate with alcohol or other CNS depressants. Also in the proposed label and in the Medication Guide, patients are warned to use extreme care while performing any task that could be dangerous or requires full mental alertness until they know whether the product has any carryover effect the next day. Patients are also warned not to engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle, for at least 6 hours after taking their second nightly dose of sodium oxybate.

5.2.2 Potential for Abuse, Misuse, Dependence, and Overdose

In the fibromyalgia clinical studies with sodium oxybate, there were no adverse events indicative of abuse, dependence, misuse, or severe withdrawal symptoms with use of sodium oxybate. There was one event of overdose in which a patient with narcolepsy took 15 times the maximum dose; the patient recovered without sequelae.

The proposed label has a boxed warning noting that GHB is a known drug of abuse and that abuse of GHB has been associated with important CNS adverse events. The proposed risk mitigation for sodium oxybate focuses on the established controls against diversion, abuse, and misuse that are inherent in sodium oxybate's status as a Schedule III controlled substance and on education of prescribers and patients about the risks of abuse and diversion.

Prescription and distribution of the product will be through a tightly controlled, validated process (see [Section 5.3.2](#), Elements to Assure Safe Use), which includes checks to prevent prescription of more than one sodium oxybate-containing product at a time and to monitor for potential abuse or misuse. The proposed label and Medication Guide instruct prescribers, pharmacists, and patients about safe use, handling, and disposal of the product and state clearly that patients should not give or sell their medication to anyone else. The proposed label also discusses the appropriate handling of overdose. To ensure prescriber, pharmacist, and patient awareness of the potential for and risks associated with abuse, the boxed warning in the proposed label notes the potential for abuse as well as CNS- and respiratory-depressant effects.

5.2.3 Product Labeling Components

The full product labeling for sodium oxybate for fibromyalgia is an essential part of the overall education of prescribers and patients.

5.2.3.1 Full Prescribing Information

The full prescribing information (PI) communicates information about the potential risks of the product, including but not limited to the primary risks described in [Sections 5.2.1](#) and [5.2.2](#). The PI also notes that the product is supplied under the terms of a REMS and provides

information about the appropriate prescribing and safe use of the product. The PI will also be available through the product website.

5.2.3.2 Packaging/Bottle Labeling

The carton will contain a statement instructing the pharmacist to include a Medication Guide with each prescription. It will also state that the active ingredient in sodium oxybate for fibromyalgia is the same as that in Xyrem. Additional language on the oral syringe will instruct users to use only this syringe with sodium oxybate for fibromyalgia, to ensure proper dosing.

5.2.3.3 Medication Guide

The Medication Guide is an essential tool in educating patients about the potential risks of the product. The Medication Guide also provides important information for patients about the safe use, handling, and disposal of the product, with a strong statement against diversion. Patients are instructed to read the entire guide before first taking the product and at every prescription refill because there may be new information.

5.3 REMS Elements

5.3.1 Medication Guide

A Medication Guide is dispensed with each product prescription. The product carton will contain a statement instructing the pharmacist to include a Medication Guide with each prescription.

A Medication Guide will be included with each carton of the product sent from the manufacturer to the certified pharmacy, which will enable the pharmacy to provide it directly to the patient with every shipment. Pharmacies certified in the fibromyalgia program (see Section 5.3.2) must agree to provide a Medication Guide with each shipment (prescription fill) and to counsel the patient to read it because information may have changed. The Medication Guide will also be available on the product website.

5.3.2 Elements to Assure Safe Use

The sodium oxybate REMS includes a controlled system that works to ensure proper distribution, prescribing, dispensing, and use of sodium oxybate in the treatment of fibromyalgia. The program is designed to provide safe and adequate access for patients, while not placing an undue burden on prescribers. The program is also designed to appropriately and effectively monitor and minimize opportunities for abuse, misuse, and diversion.

The REMS program integrates the following elements to assure the safe use of sodium oxybate for fibromyalgia:

1. The product will be prescribed only by healthcare providers who are specially certified through enrollment in the program.

The initial product prescription is filled only after the enrolled prescriber has received and read the educational materials for prescribers. The educational materials are distributed to prescribers by representatives of Jazz Pharmaceuticals. The materials are also available to prescribers from the central processing function (CPF) or over the internet.

- Certification for prescribers of sodium oxybate for fibromyalgia requires prescribers to enroll in the program and to attest to the following:

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- i. I have read the Prescribing Information Highlights for sodium oxybate for fibromyalgia.
 - ii. I understand that the product is approved for the treatment of fibromyalgia.
- Prescribers complete a one-time Prescriber Enrollment Form and send the form to the CPF via facsimile or other convenient method (including email or other electronic means of communication that is consistent with current State or Federal guidelines).
- Prescribers complete a one-time patient enrollment using a Prescription Form for each patient and send it to the CPF by facsimile or other convenient method. The prescriber verifies the following:
 - i. I verify that the patient has been educated on preparation, dosing, and scheduling of the product.
 - ii. I verify that the patient is not taking other sodium oxybate-containing products.
 - ii. I verify that the patient has received his/her own copy of the patient materials. (Optional—may be provided by CPF.)

The purpose of certifying prescribers is to ensure that they are familiar with the risk and benefit information and have made an informed prescribing choice for an individual patient. Further, the prescriber enrollment provides assurance that prescribers who are writing the product are licensed and not restricted in their ability to prescribe Schedule III controlled substances under their DEA registration.

2. All prescription forms are delivered to a CPF to be validated.

The CPF verifies that the prescriber is eligible to prescribe sodium oxybate for fibromyalgia by validating the prescriber's DEA registration via an appropriate database, including confirming that the prescriber has an active DEA number and determining whether any actions are pending against the prescriber.

The validation process includes verification of the following:

- Current prescriber enrollment
- Patient enrollment
- Patient education and counseling; if required, the CPF will provide education on product preparation, dosing, and scheduling
- Patient receipt of Medication Guide
- Patient verification that they are not taking any other sodium oxybate-containing products
- Cross-checking with the Data Coordination Center (DCC) to ensure that the patient is not receiving more than one sodium oxybate-containing product at the same time
- Certification of pharmacy enrollment

Tracking of early refills will be done through the CPF and concatenated by the DCC to allow for trending of overall patterns of early refills across these sodium oxybate products to check for changes in rates of potential abuse and misuse.

The purpose of a CPF is to provide a single source for the patient and prescriber enrollment. In addition, the patient enrollment provides mitigation to the risk of abuse and misuse by ensuring that patients are not collecting overlapping prescriptions from more than one prescriber; it also allows for verification of patient education and provides another opportunity for patients to ask questions about the information that is provided to them.

3. Sodium oxybate for fibromyalgia will be dispensed only by pharmacies that are specially certified. No certified pharmacy will dispense both sodium oxybate for fibromyalgia and Xyrem to prevent confusion of products and product information and materials (oral syringes, pharmacy vials, and Medication Guides). Xyrem will only be dispensed from an exclusive central pharmacy.

- Sodium oxybate for fibromyalgia is distributed and dispensed through certified pharmacies that are contracted to fulfill this function and registered with the CPF.
- Jazz Pharmaceuticals or its designee will certify and decertify pharmacies. The CPF will educate certified pharmacies on dispensing and other reporting requirements.
- The CPF will provide validated prescriptions to the certified pharmacy for dispensing.
- Pharmacies will report suspicious requests, including early refills, to the CPF.
- The certified pharmacy dispenses the drug after ensuring receipt of a validated prescription.

The purpose of certified pharmacies is to ensure they know of and comply with the approved REMS process. Following refills closely adds a burden to the healthcare system, while it helps to minimize the potential for abuse and misuse.

4. Sodium oxybate for fibromyalgia will be dispensed only to patients with documentation of safe use conditions.

- Upon receipt of the initial Prescription Form, the CPF verifies that the patient has received patient education materials (the Medication Guide) from the prescriber. If that has not occurred, the CPF provides verbal education to the patient and supplies the Medication Guide to the patient. The CPF verifies that the patient is not taking any other sodium oxybate-containing products. The CPF also cross-checks with the DCC that the patient is not taking any other sodium oxybate-containing products.
- All patient enrollment information is verified before the initial prescription is filled.
- The first prescription shipment is limited to a one-month's supply of the product.
- Patients do not receive more than 3 months' supply of the product per shipment.

The purpose of this element is to ensure that patients have received the educational materials. The PI clearly articulates and emphasizes the product risks. The Medication Guide completely and concisely informs patients about the risks and precautions, as well as directions for safe use. The limitation on the duration of the prescriptions is to ensure that prescribers evaluate if patients are responding appropriately to the therapy and if they should

continue treatment. The verification of other sources of sodium oxybate ensures that patients are not receiving drug from more than one prescription at the same time.

5. Implementation System

The Implementation System includes the following:

- Jazz Pharmaceuticals will maintain or monitor the procedures for the DCC database containing all certified healthcare providers and patients.
- Jazz Pharmaceuticals will monitor the distribution of the product to ensure that it is being distributed only by authorized distributors to certified pharmacies. Deviations will be documented and investigated as required. Certified pharmacies or distributors with significant deviations from the required REMS procedures will be de-certified and no longer able to receive shipments until they can demonstrate that their practices will conform to the REMS requirements.
- Certified pharmacies will report any suspicions of misuse or abuse or diversion of the product to the CPF, which will provide reports to the DCC for concatenation and review of such events for changes in rates (trends) across the two sodium oxybate products. This information will be provided to Jazz Pharmaceuticals. The certified pharmacies will follow procedures that seek to identify and minimize potential misuse, abuse, or diversion through practices that include the following:
 - Prescription refills are permitted in the number specified in the original prescription. If a patient requests a prescription refill before the anticipated refill date, the pharmacist verifies the legitimacy of the request and reports the early refill request to the CPF if the patient has made more than one early refill request or if the request is considered to be suspicious. Certified pharmacies will route suspicious requests for early refills through the CPF. The CPFs will provide data to the DCC to concatenate these data for overall trending of events that may indicate possible misuse or abuse of the products.
 - If the patient's drug is lost, stolen, destroyed, or spilled, the certified pharmacy documents the loss and replaces the prescription to the extent necessary to fulfill the original prescription. In such cases, the pharmacist may contact the prescriber to determine whether the prescriber has any special concerns with regard to the replacement refill request and has the discretion to grant or refuse to grant such replacement refill requests, as appropriate. The CPF will be notified of the early refill request. New supplies are provided to the patient only if the pharmacist and prescriber are in agreement. Note: Reasonable variation in refill dates is allowed without verification to accommodate patient scheduling needs.
 - Repeat instances of lost, stolen, destroyed, or spilled prescriptions are flagged for monitoring, and future instances are thoroughly questioned and reported to the CPF.
- Jazz Pharmaceuticals will monitor the CPF to verify that the product is being provided only after documentation of safe use conditions is provided to enrolled patients. Deviations will be documented and investigated as appropriate.
- Jazz Pharmaceuticals will periodically monitor the safety databases, such as those

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established by the Drug Abuse Warning Network (DAWN), the American Association of Poison Control Centers, The National Forensic Laboratory Information System, and the National Drug Threat Assessment, for any abuse or misuse of sodium oxybate.

- Based on the monitoring and evaluation of these Elements To Assure Safe Use, Jazz Pharmaceuticals will take reasonable steps to work to improve implementation of these elements. Jazz Pharmaceuticals periodically will provide FDA with summarized information regarding the results of monitoring and improvements as they are implemented.

6. Assessment Plan

Jazz Pharmaceuticals will submit a REMS assessment for sodium oxybate for fibromyalgia to the FDA, following approval of the REMS, at 6 months, 12 months, and then annually for the first 3 years, with a final report at 7 years following implementation of the REMS. The assessment for the first period will include surveys of:

- Prescribers, as well as pharmacists from the certified pharmacies, to assess knowledge of key REMS messages, including: (a) indication; (b) known risks; (c) understanding of the program.
- Patients, to elicit understanding of key REMS messages about the safe use of the product from the Medication Guide, including: (a) dosing; (b) known risks; (c) keeping their medication safe.

Data from the surveys will be used to determine whether adjustments should be made to the information provided to prescribers and patients.

5.4 REMS Summary

The comprehensive REMS proposed for sodium oxybate for treating fibromyalgia provides a balance of mitigation of societal and individual patient risk. At the same time, it works to avoid unduly impeding patient access to the product when a prescriber has decided that a patient is an appropriate candidate for therapy. Patients who use the existing system report that they find it to provide good support and to be of benefit to them. The balance in the REMS is tilted toward mitigation. The REMS uses a proven system, shown over the past 8 years, to limit the risks of sodium oxybate therapy both for the individual and for society as a whole. Jazz Pharmaceuticals will continue its commitment to appropriately market the product, including not engaging in television promotion to consumers, effectively operating the REMS, and implementing improvements to the system.

6 BENEFIT RISK PROFILE

Fibromyalgia is a chronic pain condition affecting 3 to 6 million people in the United States. In addition to unremitting and often severe physical pain, patients suffer fatigue and disturbed sleep that lowers their pain threshold, an impaired ability to function in everyday life, financial hardship from lowered productivity and medical costs, and emotional and mental duress, often exacerbated by years of misdiagnosis and skepticism.

The impact of fibromyalgia on a patient's life is best assessed scientifically by the use of the Fibromyalgia Impact Questionnaire (FIQ), a widely used, validated instrument that covers multiple aspects of impact: physical impairment, feeling good, work missed, difficulty with work, pain, fatigue, tiredness upon awakening, stiffness, anxiety, and depression ([Burckhardt et al. 1991](#)). The FIQ score is a strong predictor of economic and clinical outcomes, such as disability and improvement ([Bennett et al. 2009](#)). Patients with moderate to high FIQ scores (50 to 74 on a 0-100 scale) have been shown to have work disability rates as high as 35%, and those with scores above 75 have work disability rates as high as 83% ([White et al. 1999](#)).

Sodium oxybate offers an important new therapeutic option for patients who continue to seek broad symptom relief despite current therapies, whose primary pain relief needs are not met by other approved agents, or who need a different tolerability profile. For a modest but significant portion of the fibromyalgia population, sodium oxybate has the potential to provide substantial benefits across multiple symptoms, including pain, fatigue, sleep, and ability to function. This application seeks approval for the 4.5 and 6 g/night doses of sodium oxybate, with a proposed indication for the treatment of fibromyalgia.

6.1 Benefits of Sodium Oxybate Treatment

6.1.1 Multimodal Efficacy

In controlled clinical trials, sodium oxybate treatment relieved multiple symptoms of fibromyalgia in a significantly greater proportion of subjects compared with placebo. In these subjects, who presented with high levels of pain and fatigue, disturbed sleep, and impaired daily and physical function, sodium oxybate significantly reduced pain and fatigue, and improved daily living, physical functioning, sleep, and subjects' overall assessment of their condition. These robust and clinically relevant results were seen in two adequate, well-controlled Phase 3 trials, supported by a Phase 2 placebo-controlled trial, and consistent with earlier work in fibromyalgia patients.

6.1.2 Benefits across Studies, Core Domains, and Subpopulations

Each of the two Phase 3 controlled studies achieved their primary endpoints, using relevant, responsive, and validated outcomes. In addition, each study demonstrated the effectiveness of sodium oxybate in a series of sequentially tested secondary endpoints and a composite endpoint comprising global response, pain, and function. Benefits were thus seen across a broad range of endpoints that include the core symptom domains for fibromyalgia identified by both patients and physicians as clinically important. The uniformity of effect size demonstrates the consistent benefit of sodium oxybate across the symptoms of pain, fatigue, sleep, and health-related quality of life.

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Benefits were observed across subpopulations, including in subgroups based on disease severity and time since first symptoms, indicating that sodium oxybate is effective in reducing pain and improving function regardless of disease severity or duration of symptoms.

6.1.3 Clinical Relevance and Magnitude of Effect

Substantial effects were seen not only in the proportion of subjects showing improvement, but in the magnitude of change. At study endpoint, approximately 30% of subjects in each dose group experienced at least 50% reduction in pain on the pain VAS (roughly twice the rate of placebo). Separation from placebo was seen at all levels of pain relief in the two Phase 3 controlled studies: up to 80% and 90% in the two Phase 3 controlled studies, 06-008 and 06-009, respectively. A criterion of 50% pain relief on the pain VAS was defined as substantial ([Dworkin 2008](#)). These responses are therefore clinically meaningful, particularly to patients with long-term, unremitting pain. Improvements in function (using the FIQ and SF-36), fatigue, and sleep disorder met or exceeded minimal clinically important differences.

6.1.4 Early Onset and Maintenance of Effect

Furthermore, substantial benefits were observed early in treatment and persisted throughout the 14-week controlled studies and over the long term. Reductions in pain and fatigue were seen as early as one week after treatment initiation, and improvements in daily living, physical function, and sleep were seen at the first time points measured. Interim analysis of a 38-week extension study indicated beneficial effects were maintained for up to one year of treatment.

6.1.5 Manageable Dosing Regimen

Based on compliance data, subjects had no difficulty following the dosing regimen and awakening for their second dose during the night. Improvements in sleep and fatigue occurred despite this dosing regimen.

6.1.6 Summary of Benefits for Patients with Fibromyalgia

Benefits for patients include the following.

- Substantial improvement across multiple symptom domains regardless of disease severity and duration of symptoms
- Improvements in pain and fatigue seen as early as one week—an important benefit for patients with high levels of pain and fatigue
- Improved sleep
- Maintenance of beneficial effect (data for up to one year of treatment)
- A single agent that can address the constellation of fibromyalgia symptoms
 - Less complex dosing regimen for patients who currently use multiple medications to manage their various symptoms polypharmacy
 - Potential for fewer drug interactions with a single agent taken in the recommended regimen versus multiple agents
- A unique mechanism of action, as a GABA_B and GHB receptor agonist, that provides an important therapeutic alternative to current therapies
- A well-documented safety and tolerability profile (see [Section 6.2](#)), with nearly 8 years of postmarketing experience

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6.2 Risks to the Individual Patient

As with any drug treatment, there are risks associated with sodium oxybate treatment, some of which derive from properties related to its effectiveness. Clinical studies in 1060 sodium oxybate-treated patients with fibromyalgia and 781 patients with narcolepsy, together with postmarketing experience in more than 35,000 patients in the US (31,645 patient-years of experience), provide a significant body of data about the safety and risk profile for sodium oxybate. The nearly 8 years of postmarketing experience also provides substantial information about how the risk communication provided by the REMS program helps to mitigate these risks.

For the individual patient, the primary risks of sodium oxybate treatment are those identified in the boxed warning for the current sodium oxybate product and in the boxed warning for the proposed label for sodium oxybate for fibromyalgia: the known CNS- and respiratory-depressant effects of sodium oxybate. The label also warns about the potential for suicidality and depression. Other risks include other adverse events seen in the clinical trials in patients with fibromyalgia. No new significant risks have been identified in the fibromyalgia patient population beyond those seen in clinical trials with narcolepsy and in nearly 8 years of postmarketing experience with sodium oxybate in approximately 35,000 patients.

The first mitigation of any pharmaceutical risk is to clearly communicate that risk to prescribers through physician labeling and to patients through the Medication Guide, both of which are carefully developed with the FDA. The following section summarizes risks currently conveyed in the proposed prescribing information for sodium oxybate for the treatment of fibromyalgia. Because we have not completed the FDA review process, final language for the label has not been completed with FDA and we expect to work with them to finalize appropriate language for risk communication.

6.2.1 CNS- and Respiratory-Depressant Effects

The CNS-depressant effects of sodium oxybate have the potential to cause respiratory depression and decreases in the level of consciousness, including rare instances of coma and death. The respiratory-depressant effects of sodium oxybate were assessed in patients with narcolepsy and in patients with obstructive sleep apnea. There were no dose-related changes in oxygen saturation in the narcolepsy trial, and no increase in the overall severity of sleep-disordered breathing or worsening in the severity and duration of oxygen desaturation in the obstructive sleep apnea trial. Among the 874 patients receiving sodium oxybate in the three controlled trials in fibromyalgia, isolated events of apnea, respiratory rate decreased, and hypoventilation were reported. Dyspnea with cyanosis and serious related adverse events of sleep paralysis and unresponsive to stimuli occurred in one patient after the first nightly dose and led to study discontinuation. The proposed risk mitigation for this risk focuses on the education of prescribers and patients to make them aware of the risks for CNS and respiratory depression and provide important information about the safe use of the product. Physicians will be required to certify their understanding of this information before enrolling in the REMS program. As with all drugs with central depressant effects, physicians are informed about the need to appropriately evaluate patients with compromised respiratory function who are prescribed sodium oxybate.

The proposed label also carries a boxed warning about the CNS-depressant effects of sodium oxybate and warns against the use of sodium oxybate with alcohol or CNS depressants. In the 874 subjects taking sodium oxybate in three controlled trials in fibromyalgia, treatment-emergent adverse events of somnolence occurred in 3.2% and 5% of patients taking 4.5 and 6 g sodium oxybate, respectively, compared to 2.8% taking placebo. Other events potentially related to CNS depression, including depressed level of consciousness and unresponsiveness, each occurred in <1% of patients taking sodium oxybate. Events of fall and road traffic accident were low (each <1%) and similar between patients taking sodium oxybate and those taking placebo. The impact of adverse CNS-depressant effects is potentially decreased by the nighttime dosing regimen. Due to sodium oxybate's short half-life, which limits the duration of exposure, the level of next-day impairment is relatively low. The proposed risk mitigation for this product focuses on strong label warnings and education of patients and physicians about the potential for CNS-depressant effects. The proposed label will include a boxed warning for CNS depression and state that sodium oxybate should not be used with alcohol or CNS depressants. In the proposed label and the Medication Guide, patients are warned to use extreme care while performing any task that could be dangerous or requires full mental alertness until they know whether the product has any carryover effect the next day. Patients are also warned not to engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle, for at least 6 hours after taking their second nightly dose of sodium oxybate.

6.2.2 Potential for Suicidality and Depression

In the Phase 3 fibromyalgia studies, six subjects endorsed multiple items on the BDI-II question 9 or the MINI suicidality module, and 30 cases in which subjects endorsed a single item on these instruments, indicating either a past history of suicidal behavior or current low level of potential suicide risk.

Among the 874 subjects taking sodium oxybate in three controlled fibromyalgia trials, adverse events of major depression and depressed mood occurred in <1% of patients, and a single event of depression with suicidal ideation was reported, leading to study discontinuation. In all treatment groups in the Phase 3 placebo-controlled studies, results from the MINI major depressive episode module demonstrated reductions from baseline in the number of subjects with responses indicative of a major depressive episode. At study endpoint in the three controlled trials in fibromyalgia, the number of subjects with responses indicative of a major depressive episode (MINI major depressive episode module), the mean total scores for symptoms of depression (BDI-II), and the percentages of subjects with total scores indicative of more than minimal and severe depressive symptoms (BDI-II) had all decreased.

Patients with fibromyalgia may have comorbid symptoms of depression that should be kept in mind during treatment with sodium oxybate. Therefore, the proposed risk mitigation for this product focuses on the education of prescribers and patients regarding the safe and appropriate use of this product and awareness in the setting of potentially emergent depression or suicidality. The proposed label states that the emergence of depression in patients treated with sodium oxybate requires careful and immediate evaluation, and that patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking sodium oxybate.

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6.2.3 Other Potential Risks

6.2.3.1 Drug Interactions

The short half-life of sodium oxybate limits drug exposure, resulting in a subsequent low level of next-day impairment. The boxed warning in the proposed label warns against use with alcohol or other CNS depressants. Sodium oxybate does not undergo appreciable first-pass hepatic metabolism, does not inhibit cytochrome P450 isoenzymes, has no active metabolites, and is cleared almost entirely by biotransformation (via the Krebs cycle) to carbon dioxide, which is then eliminated by expiration, and water. As a result, the risk for drug interactions and for drug elimination problems secondary to hepatic and renal dysfunction is relatively low. No pharmacokinetic drug-drug interactions or clinically significant pharmacodynamic interactions were seen between sodium oxybate and drugs from classes commonly used in the fibromyalgia patient population, including the antidepressant duloxetine, the benzodiazepine lorazepam, and the opioid tramadol. In addition, no pharmacokinetic interactions were seen with zolpidem, protriptyline, modafinil, omeprazole, and fomepizole.

6.2.3.2 Sodium Intake

Physicians must exercise care in prescribing sodium oxybate to individuals who may be sensitive to sodium intake (e.g., those with heart failure, hypertension, or compromised renal function). The proposed product label will contain an appropriate caution for patients and prescribers.

6.2.3.3 Weight Loss

Mean body weight and body mass index decreased in patients on sodium oxybate (versus minimal increases in those on placebo) and continued over time in the fibromyalgia clinical trials. Although this patient population tends to be overweight, the magnitude of decrease (mean decreases of -4.81 kg in body weight and -1.75 kg/m² in BMI at Week 52) could potentially pose a risk to an individual who is underweight at inception of therapy or who has difficulty maintaining adequate weight. Changes in body weight and BMI will be described in the Adverse Reactions section of the proposed product label.

6.3 Societal Risks

6.3.1 Potential for Abuse, Misuse, Dependence, and Overdose

ABUSE AND MISUSE

The commercial sodium oxybate product has a boxed warning noting that GHB is a known drug of abuse. In the fibromyalgia clinical studies with sodium oxybate, there were no adverse events indicative of abuse, dependence, misuse, overdose, or severe withdrawal symptoms. This finding is consistent with the cumulative postmarketing experience, which includes an extremely low incidence rate (0.01 per 100-patient years) of abuse or dependence and an even lower incidence of drug-facilitated sexual assault. These extremely low rates suggest a very low risk profile for abuse-related events. Concern that sodium oxybate might present the same risk profile as illicit GHB is not supported by the available data.

While illicit use of GHB has been described in the media and in the literature, rates of abuse reported by Drug Abuse Warning Network (DAWN) and the American Association of Poison Control Centers are low compared with both prescription and illicit drugs of abuse and have declined precipitously since the early 1990s. Notably, the decline in rates of abuse

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with GHB was not affected by the market introduction of sodium oxybate for the treatment of cataplexy in narcolepsy in 2002.

- Incidences of hospital emergency department reports of events involving GHB and GHB-related analogs are among the lowest of reported drug-associated events, and decreased by about 33% from 2000 to 2002 (from 4969 to 3330 visits; [The Drug Abuse Warning Network \[DAWN\] Report July 2004](#)). For 2004, 2005, 2006, and 2007, the numbers of visits involving GHB totaled 1789, 1036, 1084, and 2207; the differences between the 2007 report and that for each of the preceding 3 years was not statistically significant ([Substance Abuse and Mental Health Services Administration \[SAMHSA\], DAWN 2010](#)).
- Reports of GHB exposures from the American Association of Poison Control Centers decreased from 1,916 (involving 6 deaths) in 2001 to 800 (without any deaths) in 2003 and to 554 (1 death) in 2005 ([Lai et al. 2006](#)).
- Annual use of GHB among 8th graders and 10th graders remained relatively stable from 2004 to 2005, but 12th graders reported a significant decrease. In 2005, 0.5% of 8th-graders, 0.8% of 10th graders, and 1.1% of 12th graders reported any use in the previous 12 months ([Johnston et al. 2008](#)).
- The percentage of items seized in law enforcement situations that tested positive for GHB or its precursor gamma-butyrolactone (GBL) decreased by 83% from 2000 to 2007 ([NFLIS 2007](#)).

Literature published between 1961 and 30 June 2009, was reviewed to examine the reported extent of GHB use in drug-facilitated sexual assaults ([Nemeth et al. 2010](#)). In 11 studies, with a wide range of drugs reported in sexual assault cases, GHB was detected in 0.2% to 4.4% of reported sexual assaults. The authors note that their results do not support widespread labeling of GHB as a date rape drug.

In studies, GHB abuse is moderated by its negative effects. In dose-effect comparison studies in recreational drug users, the magnitude of effect for GHB on reported positive subjective effects and liking ratings was similar to that of other sedative drugs, such as ethanol, and intermediate to a benzodiazepine and barbiturate ([Abanades et al. 2006, 2007](#), [Carter et al. 2006b](#)). This intermediate rating and the low incidence of abuse may be due in part to GHB's significantly greater negative subjective effects, including nausea and sedation, compared to the other drugs. Animals demonstrate rates of GHB self-administration similar to those with saline ([Beardsley et al. 1996](#), [Woolverton et al. 1999](#)).

OVERDOSE

Information regarding overdose with sodium oxybate is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances, the co-ingestion of other drugs and alcohol is common, and may influence the presentation and severity of clinical manifestations of overdose. In addition, overdose with GHB may be indistinguishable from overdose with other drugs, or from several other medical conditions that result in similar symptoms ([Couper et al. 2004](#)).

Dietze and colleagues ([2008](#)) performed a retrospective analysis of a database of ambulance service records on attendances at nonfatal drug overdoses, March 2001 through

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October 2005, in Melbourne Australia. Of 618 GHB-related ambulance attendances, 362 involved GHB only and 256 involved concurrent use of GHB and other drugs. There were 3723 heroin overdoses observed during the same period. The number of GHB-related attendances increased by around 4% per month, which was a higher rate of increase than for heroin overdose attendances. Most patients were younger than 25 years, were attended to in public spaces, and had a Glasgow Coma Scale <10. Around 90% of patients were transported to hospital, compared with 21% of heroin overdose attendances.

Kintz and colleagues (2005) documented the first reported death from GHB overdose in France and quantified drug present in different body fluids. Reed & Clegg (2006) described the occurrence of paroxysmal sympathetic surge in a patient who had overdosed on GHB. Clark & Schofield (2005) reported on abuse of GHB with anabolic steroids and ephedra which led to dilated cardiomyopathy and acute liver failure in a 40-year-old body builder. Ulrich and colleagues (2005) reported on rhabdomyolysis, acute compartment syndrome, and renal failure after ingestion of cocaine, benzodiazepines, and GBL (which is rapidly metabolized to GHB) or GHB in a 26-year-old nurse who was attempting suicide. Liechti & Kupferschmidt (2005) commented on this case, noting that the combined use of stimulant drugs with GBL or GHB may increase the risk for rhabdomyolysis due to prolonged coma and immobilization. While Zvosec and Smith (2005) suggested that agitation, combativeness, and bizarre or self-injurious behavior were previously unidentified indicators of GHB toxicity, Wood and colleagues (2006) questioned the methodology of their study (citing possible unexamined drug interactions). Brown and Nanayakkara (2005) reported on a case of accidental ingestion of acetone-free nail polish containing GBL by a 15-month-old child, which led to coma and cardiorespiratory collapse.

DEPENDENCE

Cases of severe dependence and craving for GHB have been reported. 1,4-butanediol (1,4-BD) is an industrial solvent that is metabolized to GHB. Wojtowicz and colleagues (2008) reported a case of withdrawal from 1,4-BD lasting 6 days and complicated by new-onset seizures and rhabdomyolysis. In addition, the authors conducted a systematic review of the English literature pertaining to withdrawal from GHB, 1, 4-BD, and GBL, identifying 27 studies with 57 episodes of withdrawal. Thirty-six cases (63%) involved GHB, 3 cases (5%) involved 1, 4-BD, and 18 cases (32%) involved GBL. The most common symptoms were tremor (67%), hallucinations (63%), tachycardia (63%) and insomnia (58%). Seizures and rhabdomyolysis each occurred in 7% of cases, but only one death occurred.

Data suggest that the likelihood of developing physical dependence to sodium oxybate at therapeutic doses is low (Tarabar & Nelson 2004). Addolorato and colleagues (2005) commented that withdrawal symptoms reported in the literature occurred at doses ≥ 18 g/day, well in excess of doses used therapeutically. Trendelenburg and colleagues (2004) reported on a patient who self-treated his social phobia with GHB obtained via the internet and administered at a dose of 20 g/day. The social phobia resolved, but he experienced withdrawal symptoms when he attempted to wean himself from GHB. Discontinuation of GHB was accomplished with transient use of diazepam (up to 40 mg/day).

Both epidemiological and laboratory studies have reported that frequent, around-the-clock patterns of GHB administration can produce physical dependence, as evidenced by a withdrawal syndrome (Abanades et al. 2007). Physical dependence (characterized by the

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emergence of withdrawal signs and/or symptoms upon cessation of use) was reported with daily use of illicit GHB at supratherapeutic doses of 18 to 250 g/day (Dyer et al. 2001, Glasper et al. 2005). In patients who ingested these high doses of illicit GHB around the clock, withdrawal signs and symptoms included psychosis, agitation, tachycardia, hypertension, delirium with auditory and visual hallucinations, diaphoresis, nausea, and vomiting. The onset of these reactions occurred within 1 to 6 hours after the last dose of GHB and lasted 5 to 15 days. One death of a hospitalized patient occurred as the withdrawal symptoms were resolving (Glasper et al. 2005).

MITIGATION OF RISKS OF ABUSE, MISUSE, OVERDOSE, AND DEPENDENCE

The proposed risk mitigation for this product focuses on the controls against diversion, abuse, and misuse deriving from sodium oxybate's status as a controlled substance and on education of prescribers and patients about the risks of abuse and diversion. The proposed REMS program for the patient population for this product, which is estimated to peak at 120,000 patients in 2018, parallels the current risk management program for Xyrem, which has been effective in minimizing the potential for abuse and diversion, including providing for early detection of individual and intrahousehold abuse through checks on early refill requests. The central database and coordinating function is designed to ensure that patients do not receive both sodium oxybate products. The proposed label will discuss appropriate handling of overdose. A boxed warning in the proposed label will note the potential for abuse.

6.3.2 Other Potential Risks

The twice-nightly dosing regimen, which requires patients to prepare their second dose and leave it by their bedside at night, poses the potential risk of accidental ingestion by children or pets. The proposed mitigation for this risk focuses on educating prescribers and patients about the potential for inadvertent exposure and provision of child-resistant containers. The proposed label will contain language addressing this risk and recommending care in storage and handling. Each bottle of sodium oxybate will be provided with a child-resistant cap, and the two empty pharmacy containers provided with each prescription and intended for holding the two nightly doses also have child-resistant lids.

6.4 Benefit/Risk Conclusion

Although recent approvals of three fibromyalgia medications have provided some relief for some patients, no product helps all patients, relieves pain completely, or addresses all the combined burdens of pain, fatigue, disturbed sleep, and loss of function. With no single treatment that addresses all the major symptoms of fibromyalgia, physicians and patients employ a combination of different medications to manage the several primary symptoms. This approach imposes additional complexity and inconvenience, as well as the risk of additive side effects and adverse drug reactions. Patients with fibromyalgia need additional choices, including an effective therapy that can address their multiple symptoms and restore their ability to function in daily life. In the context of their ongoing need, the clinical data presented in this document are compelling.

Sodium oxybate provides multimodal benefits in the core symptom domains of fibromyalgia. Patients reported significant reductions in pain and fatigue, and significant improvements in sleep and ability to function in everyday life. These benefits were seen early, were

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maintained for up to a year of treatment, and were evident across studies and regardless of disease severity or duration. Effects were also of substantial magnitude, providing clinically meaningful improvement to patients.

Clinical trial data and postmarketing experience with the marketed sodium oxybate product in approximately 35,000 US patients provide strong support for the safe use of the product and document the low incidence of events of CNS and respiratory depression, suicidality and depression, and abuse. Nevertheless, as with any drug treatment, there are risks associated with sodium oxybate treatment, some of which derive from properties related to its effectiveness. The proposed REMS program for sodium oxybate provides mitigations that exceed those for high-risk drugs such as opiates. In clinical trials in fibromyalgia and narcolepsy and in postmarketing use, risks to the individual patient and societal risks have been safely managed by appropriate dosing and administration; prescriber and patient education about the risks of CNS and respiratory depression; clear language in the proposed product label about contraindications and use in specific populations; appropriate warnings and precautions about suicidality and abuse potential; an effective risk management program; and the restrictions that derive from sodium oxybate's status as a Schedule III controlled substance. The proposed REMS program for sodium oxybate for fibromyalgia is modeled on the risk management program for Xyrem, which has functioned effectively for nearly 8 years, while ensuring access to the appropriate patient population.

Sodium oxybate can provide a solution to the unmet needs of those patients with fibromyalgia who continue to seek broad symptom relief in spite of their current therapies, who continue to suffer pain, or who need a different tolerability profile. The choice to use sodium oxybate, as with all medicines, should be carefully made by the physician who has evaluated its potential risks to the patient and determined that the benefits for that patient outweigh the risks. Without this important new therapeutic option, physicians will have few alternatives to offer patients whose needs are not met by, or who cannot tolerate, current therapies. Patients enduring chronic pain, fatigue, disturbed sleep, and an impaired ability to perform the simple tasks of everyday living will not have access to a medication with a unique mechanism of action that has significantly reduced all these symptoms and has been used safely in clinical trials. We believe that the magnitude and persistence of benefit for multiple symptoms of fibromyalgia clearly outweigh the product's risks, particularly as mitigated by the proposed REMS program.

7 REFERENCES

- Abanades S, Farre M, Barral D, Torrens M, Closas N, Langohr K Pastor A, et al. Relative abuse liability of gamma-hydroxybutyric acid, flunitrazepam, and ethanol in club drug users. *J Clin Psychopharmacol* 2007; 27(6): 625-38.
- Abanades S, Farré M, Segura M, Pichini S, Barral D, Pacifici R, Pellegrini M, et al. Gamma-hydroxybutyrate (GHB) in humans: pharmacodynamics and pharmacokinetics. *Ann N Y Acad Sci.* 2006;1074:559–76.
- Addolorato G, Leggio L, Abenavoli L, Gasbarrini G. Gamma hydroxybutyric acid (GHB) withdrawal does not occur at therapeutic dosage. *Drug Alcohol Depend* 2005;77(2):209.
- Anderson KO. Role of cutpoints: why grade pain intensity? [Editorial] *Pain* 2005;113:5-6.
- Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum* 2004;50(9):2974-84.
- Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain* 2005;119:5-15.
- Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP Jr, Sharma U, Martin SA, et al. A 14-week, randomized, double-blind, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain* 2008;9:792-805.
- Beardsley PM, Balster RL, Harris LS. Evaluation of the discriminative stimulus and reinforcing effects of gammahydroxybutyrate (GHB). *Psychopharmacology (Berl)* 1996; 127(4): 315-22.
- Bennett RM, Bushmakina AG, Cappelleri JC, Zlateva G, Sadosky AB. Minimal clinically important difference in the fibromyalgia impact questionnaire. *J Rheumatol* 2009;36(6):1304-11.
- Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L. An internet survey of 2,596 people with fibromyalgia. *BMC Musculoskelet Disord* 2007;8:27.
- Bigatti, SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. *Arthritis Rheum* 2008; 59(7): 961-7.
- Brown JJ, Nanayakkara CS. Acetone-free nail polish removers: are they safe? *Clin Toxicol* 2005;43(4):297–9.
- Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. *J Rheumatol* 1991;728-33.
- Carter LP, Richards BD, Mintzer MZ, Griffiths RR. Relative abuse liability of GHB in humans: a comparison of psychomotor, subjective, and cognitive effects of supratherapeutic doses of triazolam, pentobarbital, and GHB. *Neuropsychopharmacol* 2006b;31:1-15.
- Chanimov M, Bahar M, Cohen ML, Brenner R, Koifman I, Grinshpon Y. Spinal anaesthesia with gamma hydroxybutyrate: A study in a rat model. *Eur J Anaesthesiol* 1999;16(5):330-8.

- Choy EH, Mease PJ. Key symptom domains to be assessed in fibromyalgia (outcome measures in rheumatoid arthritis clinical trials). *Rheum Dis Clin N AM* 2009;35:329-337.
- Clark BM, Schofield RS. Dilated cardiomyopathy and acute liver injury associated with combined use of ephedra, γ -hydroxybutyrate, and anabolic steroids. *Pharmacother* 2005;25(5):756–61.
- Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin Ther* 2008;30:1988-2004.
- Couper FJ, Thatcher JE, Logan BK. Suspected GHB overdoses in the emergency department. *J Anal Toxicol* 2004; 28(6):481–4.
- Crofford LJ, Mease PJ, Simpson SL, Young JP Jr, Martin SA, Haig GM, Sharma U. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain* 2008;136:419-431.
- Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin 1008-105 Study Group. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52:1264-1273.
- Crunelli V, Emri Z, Leresche N. Unravelling the brain targets of gamma-hydroxybutyric acid. *Current Opin Pharmacol* 2006; 6:44-52.
- Cymbalta[®] (duloxetine hydrochloride) Delayed-Release Capsules for Oral Use. US Prescribing Information. Eli Lilly & Company, February 2009.
- Dietze PM, Cvetkovski S, Barratt MJ, Clemens S. Patterns and incidence of gamma-hydroxybutyrate (GHB)-related ambulance attendances in Melbourne, Victoria. *Med J Aust* 2008 Jun 16;188(12):709–11.
- Dooley DJ, Taylor CP, Donevan S, Feltner D. Ca²⁺ channel α 2delta ligands: novel modulators of neurotransmission. *Trends Pharmacol Sci* 2007; 28(2): 75-82.
- Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9(2):105-21.
- Dyer JE, Roth B, Hyma BA. Gamma-hydroxybutyrate withdrawal syndrome. *Ann Emerg Med* 2001;37:147–53.
- Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149–58.
- Gendreau RM, Thorn MD, Gendreau JF, Kranzler JD, Ribeiro S, Gracely RH, Williams DA, et al. Efficacy of milnacipran in patients with fibromyalgia. *J Rheumatol* 2005;32:1975-1985.
- Glasper A, McDonough M, Bearn J. Within-patient variability in clinical presentation of gamma-hydroxybutyrate withdrawal: a case report. *Eur Addict Res* 2005;11:152–4.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

- Goldenberg DL. Fibromyalgia syndrome a decade later: what have we learned? Arch Intern Med 1999; 159(8):777-85.
- Goudet C, Magnaghi V, Landry M, Nagy F, Gereau RW, Pin J-P. Metabolic receptors for glutamate and GABA in pain. Brain Research Reviews 2009; 60:43-56.
- Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain 2010; 11(6):505-21.
- Hosli L, Hosli E, Lehmann R, Schneider J, Borner M. Action of gamma-hydroxybutyrate and GABA on neurones of cultured rat central nervous system. Neurosci Lett 1983;37(3):257-60.
- Jamison RN, Gracely R H, Raymond SA, Levine JG, Marino B, Herrmann TJ, Daly M, et al. Comparative study of electronic vs. paper VAS ratings: a randomized, crossover trial using healthy volunteers. Pain 2002; 99(1-2): 341-7.
- Jenkins, CD, Stanton BA, Niemcryk SJ, Rose RM. A scale for the estimation of sleep problems in clinical research. J Clin Epidemiol 1988;41(4):313-21.
- Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future: National Results on Adolescent Drug Use. Overview of Key Findings, 2007. National Institute of Drug Abuse, NIH Publication No. 08-6418, April 2008.
- Kaupmann K, Cryan JF, Wellendorph P, Mombereau C, Sansig G, Klebs K, Schmutz M, Froestl W, van der Putten H, Mosbacher J, Bräuner-Osborne H, Waldmeier P, Bettler B. Specific gamma-hydroxybutyrate-binding sites but loss of pharmacologic effects of gamma-hydroxybutyrate in GABAB(-1)-deficient mice. Eur J Neuroscience 2003; 18:2722-2730.
- Kintz P, Villain M, Pelissier A-L, Cirimele V, Leonetti G. Unusually high concentrations in a fatal GHB case. J Anal Toxicol 2005;29(6):582-5.
- Lai MW, Klein-Schwartz W, Rodgers GC, Abrams JY, Haber DA, Bronstein AC, Wruk KM. 2005 Annual Report of the American Association of Poison Control Centers' National Poisoning and Exposure Database. Clin Toxicol 2006;44:803-932.
- Liechti M, Kupferschmidt H. Reply: Rhabdomyolysis and drugs of abuse. Swiss Med Wkly 2005;135(13-14):206-7.
- Lingenhoehl K, Brom R, Heid J, Beck P, Froestl W, Kaupmann K, Bettler B, et al. Gamma-hydroxybutyrate is a weak agonist at recombinant GABA(B) receptors. Neuropharmacology 1999;38(11):1667-73.
- Lyrica[®] (pregabalin) Capsules, CV. US Prescribing Information. Pfizer Pharmaceuticals, LLC, April 2009.
- Maitre M. The gamma-hydroxybutyrate signalling system in brain: organization and functional implications. Prog Neurobiol 1997;51(3):337-61.
- Malcangio M, Bowery NG. Gamma-aminobutyric acid_B, but not gamma-aminobutyric acid_A receptor activation, inhibits electrically evoked substance P-like immunoreactivity release from the rat spinal cord *in vitro*. J Pharmacol Exper Ther 1993; 266(3): 1490-1496.

Mallinckrodt CH, Sanger TM, Dube S, De Brota DJ, Molenberghs G, Carroll RJ, Potter WZ, et al. Assessing and interpreting treatment effects in longitudinal clinical trials with missing data. *Biol Psychiatry* 2003;53:754-760.

Mathivet P, Bernasconi R, De Barry J, Marescaux C, Bittiger H. Binding characteristics of gamma-hydroxybutyric acid as a weak but selective GABA_B receptor agonist. *Eur J Pharmacol* 1997;321(1):67-75.

Mease P, Arnold LM, Bennett R, Boonen A, Buskila D, Carville S, Chappell A, et al. Fibromyalgia syndrome. *J Rheumatol* 2007;34(6):1415-25.

Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W, Palmer RH. The efficacy and safety of milnacipran for treatment of fibromyalgia. a randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2009a;36:398-409. Erratum in: *J Rheumatol* 2009;36:661.

Mease PJ, Russell IJ, Arnold LM, Florian H, Young JP, Jr., Martin SA, Sharma U. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol* 2008b;35(3):502-14.

Mease PJ. Further strategies for treating fibromyalgia: the role of serotonin and norepinephrine reuptake inhibitors. *Am J Med* 2009;122(12 Suppl):S44-55.

Mease PL, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass JM, Martin SA, et al. Fibromyalgia syndrome module at OMERACT 9: domain construct. *J Rheumatol* 2009b;36(10): 2318-2329.

Moldofsky H, Scarisbrick P, England R, Smythe H. Musculoskeletal symptoms and non-REM sleep disturbances in patients with “fibrositis syndrome” and healthy subjects. *Psychosom Med* 1975;37(4):341–51.

Moldofsky H. The significance of the sleeping-waking brain for the understanding of widespread musculoskeletal pain and fatigue in fibromyalgia syndrome and allied syndromes. *Joint Bone Spine* 2008; 75(4):397-402. Epub 2008 May 5.

National Drug Threat Assessment, National Drug Intelligence Center U.S. Department of Justice 2009, Product No. 2008-Q0317-005, December 2008.

National Forensic Laboratory Information System (NFLIS): Midyear Report 2007. US Drug Enforcement Administration, Office of Diversion Control. Washington DC, 2007.

Nemeth Z, Kun B, Demetrovics Z. The involvement of gamma-hydroxybutyrate in reported sexual assaults: a systematic review. *Online J Psychopharmacol*. May 20, 2010 as doi:10.1177/0269881110363315.

Nicholson KL, Balster RL. GHB: a new and novel drug of abuse. *Drug Alcohol Depend* 2001;63:1–22.

Pardi D, Black J. gamma-Hydroxybutyrate/sodium oxybate: neurobiology, and impact on sleep and wakefulness. *CNS Drugs* 2006;20(12):993-1018.

Reed MJ, Clegg GR. Paroxysmal sympathetic surge associated with gamma hydroxybutyrate. *Eur J Emer Med* 2006;13(1):41–2.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Ribel-Madsen S, Christgau S, Gronemann ST, Bartels EM, Danneskiold-Samsoe B, Bliddal H. Urinary markers of altered collagen metabolism in fibromyalgia patients. *Scand J Rheumatol* 2007; 36(6): 470-7.

Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlrreich MM, Detke MJ, Walker DJ, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain* 2008;136:432-444.

Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures. *Pharmacoeconomics* 1999;15:141-155.

Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. *Trends in Neurosci* 2001;24(12): 726-731.

Savella[®] (milnacipran hydrochloride) Tablets. US Prescribing Information. Forest Pharmaceuticals, Inc., July 2009.

Scharf MB, Baumann M, Berkowitz DV. The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia. *J Rheumatol* 2003;30(5):1070-4.

Scharf MB, Hauck M, Stover R, McDannold M, Berkowitz D. Effect of gamma-hydroxybutyrate on pain, fatigue, and the alpha sleep anomaly in patients with fibromyalgia: preliminary report. *J Rheumatol* 1998a;25(10):1986-90.

Sherman AD, Gebhart GF. An evaluation of the analgesia induced by morphine and gamma-hydroxybutyrate. *Arch Int Pharmacodyn Ther* 1975;213(2):195-9.

Stevens DR, Kuramasu A, Haas HL. GabaB-receptor-mediated control of GABAergic inhibition in rat histaminergic neurons in vitro. *Eur J Neurosci* 1999; 11:1148-1154.

Substance Abuse and Mental Health Services Administration [SAMHSA], Office of Applied Studies. Drug Abuse Warning Network, 2007: National Estimates of Drug-Related Emergency Department Visits. Rockville, MD, 2010.

Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Drug Abuse Warning Network. The DAWN Report: Club Drugs, 2002 Update. July 2004.

Tarabar AF, Nelson LS. The gamma-hydroxybutyrate withdrawal syndrome. *Toxicol. Rev.* 2004;23(1):45-49.

The Experience Project: I Have Fibromyalgia Group. The Experience Project; <http://www.experienceproject.com/stories/Have-Fibromyalgia/26714>. 09 July 2010.

Trendelenburg G, Heinz A, Ströhle A. γ -Hydroxybutyrate dependence with social phobia. *Am J Psychiatry* 2004;161(2):375-6.

Ulrich S, Muller V, Keel M, Seebach J. Sudden leg paralysis in a 26-year-old nurse. *Swiss Med Wkly* 2005;135(13-14):206.

US Xyrem[®] Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep* 2003;26(1):31-5.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Ware JE, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. Lincoln, RI: (1993, 2000) QualityMetric Inc.

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473–83.

Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20(10):835-43.

White KP, Speechley M, Harth M, Ostbye T. Comparing self-reported function and work disability in 100 community cases of fibromyalgia syndrome versus controls in London, Ontario: the London Fibromyalgia Epidemiology Study. *Arthritis Rheum* 1999; 42(1):76-83.

White LA, Birnbaum HG, Kaltenboeck A, Tang J, Mallett D, Robinson RL. Employees with fibromyalgia: medical comorbidity, healthcare costs, and work loss. *J Occup Environ Med* 2008; 50(1):13-24.

Wojtowicz JM, Yarema MC, Wax PM. Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. *CJEM*. 2008;10(1):69–74.

Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, Russell IJ, et al. A prospective, longitudinal, multicenter study of service utilization of costs in fibromyalgia. *Arthritis Rheum* 1997b;40(9):1560–70.

Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, Russell IJ, et al. Health status and disease severity in fibromyalgia: results of a six-center longitudinal study. *Arthritis Rheum* 1997a;40(9): 1571-9.

Wolfe F, Clauw DJ, Fitzcharles M, Goldenberg DL, Katz RS, Mease P, Russell AS, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthrit Care Res* 2010;62(5):600-610.

Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Golden berg DL, Tugwell P, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33(2):160-72.

Wood D, Gawarammana I, Greene S, Dargan P, Jones A. Insufficient evidence that agitation is common in gamma-hydroxybutyrate toxicity. *Am J Emerg Med* 2006;24(2):257.

Woolverton WL, Rowlett JK, Winger G, Woods JH, Gerak LR, France CP. Evaluation of the reinforcing and discriminative stimulus effects of gamma-hydroxybutyrate in rhesus monkeys. *Drug Alcohol Depend* 1999; 54(2):137-43.

Xyrem[®] (sodium oxybate) oral solution. US Prescribing Information, Jazz Pharmaceuticals, 2007.

Yunus. Are men (with FM) different from women? *National FM association Journal: Fibromyalgia Aware* 2009;1 20: 21.

Zvosec DL, Smith SW. Agitation is common in gamma-hydroxybutyrate toxicity. *Am J Emerg Med* 2005;23(3):316–20.

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Appendix A: Highlights of Proposed Product Labeling

Provided for illustrative purposes only: language will be revised with FDA.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Tradename™ (sodium oxybate) oral solution safely and effectively. See full prescribing information for Tradename™ (sodium oxybate) oral solution.

Tradename™ (sodium oxybate) oral solution CIII
Initial U.S. Approval: 2002

WARNING: Central nervous system (CNS) depressant effects. Should not be used with alcohol or CNS depressants. See full prescribing information for complete boxed warning.

- Respiratory depression occurred in clinical trials (5.2).
- Tradename is the sodium salt of GHB. Although abuse of sodium oxybate was not seen in clinical trials, abuse of illicit GHB is associated with important CNS adverse events, including seizure, respiratory depression, and profoundly decreased consciousness, with rare instances of coma and death (9).
- Report all serious adverse events to the manufacturer.

INDICATIONS AND USAGE

Tradename is a GABA_B and GHB receptor agonist indicated for the treatment of fibromyalgia (1).

DOSAGE AND ADMINISTRATION

Patients typically fall asleep in ~15 minutes, but sleep may come on abruptly (ie, without first feeling drowsy). Therefore take each dose while in bed (2).

- Initiate dose at 4.5 g/night (2 x 2.25 g/night) (2).
- Titrate to effect in 1.5 g/dose increments in weekly intervals to evaluate response and minimize adverse effects (2).
- Recommended doses: 4.5 or 6 g/night (2). Doses up to 9 g/night were studied in clinical trials.
- Instruct patients to allow 2 hours after eating before dosing; food reduces bioavailability of sodium oxybate (12.3).
- For patients with compromised liver function, decrease starting dose by half and monitor dose titrations closely (2.1).

If A Patient's Total Nightly Dose Is:	Take at Bedtime:	Take 2.5–4 Hours Later:
4.5 g/night	2.25 g	2.25 g
6 g/night	3 g	3 g
7.5 g/night	3.75 g	3.75 g
9 g/night	4.5 g	4.5 g
Patient notes: Divide total nightly dose into two equal doses; prepare both doses before bedtime. Dilute each dose with ¼ cup (~60 mL) water before swallowing. Take 1 st dose at bedtime, 2 nd dose 2.5 to 4 hours later. Lie down in bed after dosing (2).		

DOSAGE FORMS AND STRENGTHS

Oral solution, 375 mg/mL

CONTRAINDICATIONS

- Concomitant treatment with sedative hypnotic agents (4).
- Succinic semialdehyde dehydrogenase deficiency (4).

WARNINGS AND PRECAUTIONS

CNS-depressant effects with the potential to impair respiratory drive (5.2). Caution against hazardous occupations or activities requiring complete mental alertness or motor coordination after first initiating treatment until effects are known and for ≥6 hours after dosing (5.1). Confusion was reported; most cases resolved without intervention. Closely monitor patients with emergent or increased depression, particularly with history of depression or suicidality (5.3), and elderly patients for impaired motor/cognitive function (5.4). Parasomnias were reported (5.6). Consider sodium intake in patients with heart failure, hypertension, or impaired renal function (5.7).

ADVERSE REACTIONS

Most common treatment-emergent adverse reactions (≥5% and at least twice the incidence with placebo) in three controlled trials were nausea (19.7%), dizziness (13.7%), vomiting (7.1%), and anxiety (5.8%) (6.2). Most frequent reasons for discontinuation (≥2%) included nausea (3.5%), headache (2.5%), vomiting (2.4%), and dizziness (2.2%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals at 1-800-520-5568, jazzsafety@jazzpharma.com or FDA at 1-800-FDA-1088 or www.fda.gov/Medwatch.

DRUG INTERACTIONS

No pharmacokinetic interactions observed between sodium oxybate and duloxetine hydrochloride (HCl), tramadol HCl, lorazepam, protriptyline HCl, zolpidem tartrate, modafinil, or fomepizol. No significant inhibition of the activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A at levels much higher than seen at therapeutic doses (7).

USE IN SPECIFIC POPULATIONS

Specific populations not described under Dosage and Administration or Warnings and Precautions:

- Pregnancy Category B: This drug should be used during pregnancy only if clearly needed (8.1).
- Pediatric: Safety and effectiveness not established in patients <18 years (8.4).

See 17 for Patient Counseling Information and FDA-approved Medication Guide.

REV x/2010

Appendix B: Inclusion and Exclusion Criteria for the Phase 2 and Phase 3 Controlled Studies

STUDY OMC-SXB-26

OMC-SXB-26 Inclusion Criteria

Subjects were eligible for the trial if they:

1. Signed and dated an informed consent prior to beginning protocol required procedures.
2. Were willing and able to complete the entire trial as described in the protocol.
3. Were male or female > 18 years of age
4. Met the American College of Rheumatology criteria for Fibromyalgia:
 - Widespread pain for at least 3 months, defined as the presence of all of the following:
 - Pain on right and left sides of the body
 - Pain above and below the waist
 - Pain in the axial skeleton
 - Pain on digital palpation with approximately 4kg force in at least 11 of 18 tender point sites
5. (Study continuation) Had an average VAS pain score > 4 on a scale of 0 to 10 as recorded in the patient diary the last week before Visit 4.
6. Were willing to discontinue opiates, benzodiazepines, anticonvulsants taken for pain, antidepressants, cyclobenzaprine (Flexeril), and/or tramadol (Ultram) until completion of the study.
7. Were willing to continue all preexisting nutritional and/or exercise regimens and/or behavioral, massage, acupuncture, physical or cognitive therapies on an unchanged, consistent and regular schedule throughout the course of the study.
8. Throughout the course of the trial agreed to use only acetaminophen or over-the-counter (OTC) non-steroidal anti-inflammatory drugs (NSAIDs) as rescue pain medications and to limit the dose to the following maxima:

OTC Analgesic	How taken	Daily Maximum
Acetaminophen	650 mg or 1000 mg q4h	4000 mg
Ibuprofen	200 mg q4h (if first dose is insufficient, ONE additional 200 mg dose may be taken one hour later, and adjust to 400 mg q4h)	1200 mg
Naproxen	220 mg q 8 or 12 h OR 440 mg followed by 220 mg 12 hours later	660 mg
Ketoprofen	12.5 mg q4h (if first dose is insufficient, ONE additional 12.5 mg dose may be taken one hour later with dosing at 12.5 mg q4h thereafter)	75 mg

Each patient should take no more than **one** of these drugs during any given study day.

Formulations that add caffeine are **not** permitted.

Patients may, for cardiac protection, take no more than a single daily dose of 325 mg of aspirin. Any other use of aspirin is prohibited during this study.

9. Were willing to discontinue all prescription medications they were taking for fibromyalgia therapy.
10. Agreed to forego the ingestion of alcohol for the duration of the study.
11. Females may have been included who were surgically sterile, 2 years postmenopausal, or if of child-bearing potential, using a medically accepted method of birth control (eg, barrier method with spermicide, oral contraceptive, or abstinence) and agreed to continue use of this method for the duration of the trial.

OMC-SXB-26 Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

Had any of the following medical conditions:

1. Active rheumatic disease in addition to fibromyalgia, such as rheumatoid arthritis, osteoarthritis, or systemic lupus erythematosus which was causing pain of a severity and/or frequency sufficient to interfere with the evaluation of possible relief of fibromyalgia pain over the course of this trial.
2. Uncontrolled hypo- or hyper-thyroidism of any type
3. Unstable cardiovascular, endocrine, neoplastic (excluding localized basal cell carcinoma), gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease which would place the patient at risk during the trial or compromise the objectives outlined in the protocol
4. A history of myocardial infarction within the last 6 months
5. On their screening PSG had an Apnea Index greater than 10 per hour or an AHI (Apnea Hypopnea Index) greater than 15 per hour. Note that patients with sleep apnea, treated with CPAP (continuous positive airway pressure), were not excluded if their indices were below these thresholds while sleeping with CPAP and they are compliant with CPAP therapy. One way to evaluate CPAP compliance was by review of built-in device usage logs.
6. Psychiatric disorders, major affective or psychotic disorders, or other problems that, in the investigator's opinion, would preclude the patient's participation and completion of this trial or compromise reliable representation of subjective symptoms.
7. If a patient had to discontinue antidepressant medication taken for depression, the investigator made an evaluation as to any risks from cessation of anti-depressant therapy. If, in the opinion of the investigator, a reasonable risk of resultant patient harm existed, the patient was excluded from study participation

8. A current or recent (within 1 year) history of a substance use disorder including alcohol abuse as defined by the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)
9. A clinically significant history of seizure disorder either past or present, a history of clinically significant head trauma (ie, concussion resulting in clinically significant loss of consciousness), migraine headaches or past invasive intracranial surgery, and were taking anticonvulsant medications
10. Succinic semialdehyde dehydrogenase deficiency

Had taken any of these therapies:

11. Gamma-hydroxybutyrate (sodium oxybate) in the 30 days prior to signing informed consent
12. Any investigational therapy in the 30 days prior to signing informed consent
13. Ever taken anticonvulsants to treat epilepsy or any other convulsions

Were unwilling to stop these therapies during the course of the trial:

14. Anticonvulsants prescribed solely for pain
15. All antidepressants (including but not limited to, tricyclic antidepressants (TCAs) or serotonin-selective reuptake inhibitors (SSRIs)). Subjects taking antidepressants who were willing to discontinue these medications may participate if they agreed to follow the investigators' recommended down-titration and washout program (5 x the half life of antidepressant).
16. Sleep aids such as hypnotics, tranquilizers, sedating antihistamines (non-sedating antihistamines are permitted during the trial), benzodiazepines.

Had any of the following exclusionary clinical laboratory results:

17. Serum creatinine greater than 2.0 mg/dL
18. Thyroid stimulating hormone (TSH) outside the normal range (for example, $> 4 \mu\text{U/mL}$ or $< 0.4 \mu\text{U/mL}$ are abnormal based on the central laboratory's reference range)
19. Abnormal liver function tests (SGOT [AST] or SGPT [ALT] more than twice the upper limit of normal)
20. Elevated serum bilirubin (more than 1.5 times the upper limit of normal) Subjects known to have Gilbert's Disease (also known as Gilbert's Syndrome -causes hyperbilirubinemia with no known clinical consequence) were excepted from this exclusion criterion.
21. Pre-trial electrocardiogram (ECG) results demonstrating clinically significant arrhythmias, greater than a first degree AV block
22. Positive pregnancy test at any time during the trial

Had any of the following exclusionary socio-economic factors:

23. Pending worker's compensation litigation or related other monetary settlements

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24. Had an occupation that requires variable shift work or routine night shifts

STUDY 06-008

06-008 Inclusion Criteria

Eligible subjects met all of the following criteria:

1. Subject was able to understand the written informed consent, and signed and dated the consent form prior to beginning protocol-required procedures
2. Subject was willing and able to complete the entire trial as described in the protocol
3. Subject was a man or woman, 18 years of age or older
4. Subject met the ACR criteria for fibromyalgia at screening and at baseline
5. Subject had at least 5 of 7 days with 100% compliance on the VAS self-rated pain scale in the week prior to Visit 4 and had an average VAS pain score of $\geq 50/100$ mm as recorded in the subject diary on the 100% compliant days
6. Subject was willing to discontinue opiates, benzodiazepines, muscle relaxants (cyclobenzaprine [Flexeril[®]]), anticonvulsants, antidepressants, dopamine agonists and/or tramadol (Ultram[®]), or any other medications, herbal remedies, and/or devices being used to treat their fibromyalgia symptoms until trial completion
7. Subjects were on a consistent nutritional and/or exercise regimen and/or behavioral, massage, physical, or cognitive therapies for the last 3 months prior to baseline and agreed to not change those regimens for the duration of the trial
8. Subject agreed to use only acetaminophen (paracetamol) as rescue pain medication and to limit the dose to a maximum of 4 g/day throughout the course of the trial. Subjects may have taken a single daily dose of ≤ 325 mg aspirin for cardiac protection. Any other use of aspirin was prohibited during this trial.
9. Subject was willing to discontinue the ingestion of alcohol for the duration of the trial
10. Female subjects may have been included if they were surgically sterile or 2 years postmenopausal, but they must also have had a negative pregnancy test and were not nursing or lactating. Female subjects of childbearing potential and perimenopausal subjects may have been included but must have had a negative pregnancy test, were not nursing or lactating, and agreed to use a medically accepted method of birth control (e.g., barrier method with spermicide, oral contraceptive, or abstinence) and to continue use of this method for the duration of the trial.
11. Subject was screened for sleep apnea using the Berlin Questionnaire, and a determination of the subject's sleep apnea status was made
12. Subjects with a body mass index (BMI) ≥ 35 and < 40 kg/m² must have had an Apnea Hypopnea Index (AHI) < 15 per hour and oxygen saturation $> 80\%$, as determined by PSG at screening.

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06-008 Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. Subject had any of the following medical conditions:
 - Rheumatic disease in addition to fibromyalgia, such as rheumatoid arthritis, inflammatory arthritis, or systemic lupus erythematosus
 - Symptoms of painful osteoarthritis or symptomatic osteoarthritis (e.g., osteoarthritis associated with stiffness and muscle weakness) at screening or prior to randomization
 - Pain from traumatic injury
 - Uncontrolled hypo- or hyperthyroidism of any type
 - Autoimmune disease (with the exception of inactive Hashimoto's thyroiditis)
 - Multiple sclerosis
 - Unstable cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease
 - Current or recent (i.e., no evaluable disease within the past 5 years) neoplastic disease (excluding localized basal cell carcinoma)
 - Systemic infection
 - Any disease, disorder or condition that would have placed the subject at risk during the trial, interfered with the subject's or investigator's ability to measure change on any outcome measures and/or compromised the objectives outlined in the protocol
2. Subject had a history of myocardial infarction, transient ischemic attack, or cerebrovascular accident
3. Subject had a Major Depressive Disorder (as defined by the Mini International Neuropsychiatric Interview [MINI]), was being treated for a Major Depressive Disorder, or had a history of psychotic and/or bipolar disorder. Subjects considered for discontinuation of antidepressant medication required careful evaluation as to any risks from cessation of antidepressant therapy. If, in the opinion of the investigator, a reasonable risk of resultant subject harm existed, the subject was to be excluded from study participation.
4. Subject had any other problems that, in the investigator's opinion, would preclude the subject's participation and completion of this trial or compromise reliable representation of subjective symptoms
5. Subject had a MINI suicidality module score >0 and/or answered "yes" to the suicide question (A3-g) on the Major Depressive Episode module of the MINI and/or response ≥ 1 on Question 9 of the Beck Depression Inventory-II (BDI-II)
6. Subject had a current or past history of substance use disorder including alcohol abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders IV, Text Revision (DSM-IV-TR)
7. Subject had a clinically significant history of seizure disorder either past or present, a history of clinically significant head trauma (i.e., concussion resulting in clinically significant loss of consciousness), chronic persistent migraine headaches, or past invasive intracranial surgery

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8. Subject had known succinic semialdehyde dehydrogenase deficiency
9. Subject had participated in a previous Xyrem (sodium oxybate) clinical trial
10. Subject had received acupuncture therapy intended for the treatment of fibromyalgia within 30 days prior to baseline
11. Subject had taken GHB, sodium oxybate, or Xyrem at any time
12. Subject had taken any investigational therapy within 2 months prior to signing informed consent
13. Subject was unable to discontinue prohibited medications during the washout period and throughout the duration of the trial. Subjects able to discontinue these medications may have participated in the study if they agreed to follow the investigator's recommended down-titration and washout program prior to study entry. If a subject must have discontinued any of these therapies, the investigator must have made an evaluation as to any risks from cessation of such therapies. If, in the opinion of the investigator, a reasonable risk of resultant subject harm existed, the subject must have been excluded from trial participation. Prohibited medications included the following categories:
 - Anticonvulsants prescribed for any reason
 - All antidepressants (including but not limited to, tricyclic antidepressants, selective serotonin reuptake inhibitors, or serotonin/norepinephrine reuptake inhibitors, bupropion, trazodone), monoamine oxidase inhibitors, and monoamine oxidase-B inhibitors (such as selegiline)
 - Mood stabilizers such as lithium
 - Antipsychotic medications
 - Sleep aids such as hypnotics, tranquilizers, sedating antihistamines (nonsedating antihistamines were permitted during the trial), and benzodiazepines
 - Stimulant medications for any reason, including for attention-deficit hyperactivity disorder, such as dextroamphetamine, methylphenidate, and modafinil
 - Nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and corticosteroids (short-term use of nasal, inhaled, and topical corticosteroids unrelated to the treatment of fibromyalgia was allowed)
 - Dopamine agonists and any other Parkinson's disease medications
 - Opioids
 - All medications taken for pain, including pain associated with osteoarthritis or sleep disorders (except for allowed rescue medication)
 - Skeletal muscle relaxants
 - Chemotherapy for neoplastic disease
 - Any other medication taken by the subject for the treatment of fibromyalgia except for acetaminophen (paracetamol) up to 4 g per day
14. Subject was experiencing clinically significant medication withdrawal symptoms after the withdrawal/washout period

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15. Subject was experiencing fatigue and/or drowsiness/sedation in association with intake of allowed medications
16. Subject had an allergic reaction to GHB or sodium oxybate or any of its constituents (e.g., malic acid)
17. Subject had any of the following exclusionary clinical laboratory results:
 - Serum creatinine >2.0 mg/dL
 - Thyroid stimulating hormone (TSH) >6 µU/mL or <0.3 µU/mL
 - Abnormal liver function tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] more than twice the upper limit of normal)
 - Elevated serum bilirubin more than 1.5 times the upper limit of normal
 - Pretrial electrocardiogram (ECG) results demonstrating clinically significant arrhythmias or conduction delays
 - Positive pregnancy test at any time during the trial
 - Positive urine drug screen for drugs of abuse and/or positive alcohol test at screening or at the end of baseline
18. Subject was diagnosed with sleep apnea and was not currently on stable continuous positive airway pressure (CPAP) therapy for the last 30 days prior to baseline
19. Subject had a BMI ≥ 40 kg/m²
20. Subject was on a sodium-restricted diet
21. Subject had a visual impairment or motor disturbance which precluded the capacity to make accurate notation on the electronic diary VAS scales
22. Subject had any of the following exclusionary socioeconomic factors:
 - Pending worker's compensation litigation or other related monetary settlements or other pending litigation related to physical complaints
 - On disability or pending disability evaluation for chronic pain and/or fibromyalgia
 - An occupation that required variable shift work or routine night shifts
23. Subject had Generalized Anxiety Disorder as defined by DSM-IV-TR

STUDY 06-009

06-009 Inclusion Criteria

Eligible subjects met all of the following criteria:

1. Subject was able to understand the written informed consent, and signed and dated the consent prior to beginning protocol required procedures
2. Subject was willing and able to complete the entire trial as described in the protocol
3. Subject was male or female, 18 years of age or older
4. Subject met the ACR criteria for fibromyalgia at screening and at baseline
5. Subject had at least 5 out of 7 days with 100% compliance on the VAS self-rated pain scale in the week prior to Visit 4 and had an average VAS pain score of greater than or equal to

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50 mm/100 mm as recorded in the subject diary on the 100% compliant days, defined as days that the morning, afternoon, and evening diaries were all completed

6. Subject was willing to discontinue opiates, benzodiazepines, muscle relaxants (cyclobenzaprine [Flexeril[®]]), anticonvulsants, antidepressants, dopamine agonists and/or tramadol (Ultram[®]), or any other medications, herbal remedies, and/or devices being used to treat their fibromyalgia symptoms until trial completion
7. Subjects were on a consistent nutritional and/or exercise regimens and/or behavioral, massage, physical, or cognitive therapies for the last 3 months prior to baseline and were willing to agree to remain on an unchanged regimen throughout the duration of the trial
8. Subject agreed to use only acetaminophen (paracetamol) as rescue pain medication and to limit the dose to a maximum of 4 g/day throughout the course of the trial. Subjects may, for cardiac protection, have taken a single daily dose of 325 mg or less of aspirin. Any other use of aspirin was prohibited during this trial.
9. Subject was willing to discontinue the ingestion of alcohol for the duration of the trial
10. Female subjects may have been included if they were surgically sterile or 2 years post menopausal, but they must also have had a negative pregnancy test. Female subjects of childbearing potential and perimenopausal subjects may be included but must have had a negative pregnancy test and agreed to use a medically accepted method of birth control (eg, barrier method with spermicide, oral contraceptive, or abstinence) and to continue use of this method for the duration of the trial.
11. Subject was screened for sleep apnea using the Berlin Questionnaire, and a determination of the subject's sleep apnea status was made
12. Subjects with a body mass index (BMI) ≥ 35 and $< 40 \text{ kg/m}^2$ must have an Apnea Hypopnea Index (AHI) < 15 per hour and oxygen saturation $> 80\%$, as determined by PSG at screening or must have already been on stable continuous positive airway pressure (CPAP) therapy for the last 30 days prior to baseline and agreed to remain on CPAP for the duration of the study.

06-009 Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. Subject had any of the following medical conditions:
 - Rheumatic disease in addition to fibromyalgia, such as rheumatoid arthritis, inflammatory arthritis, or systemic lupus erythematosus
 - Symptoms of painful osteoarthritis or symptomatic osteoarthritis (e.g. osteoarthritis associated with stiffness and muscle weakness) at screening or prior to randomization
 - Pain from traumatic injury
 - Uncontrolled hypo- or hyperthyroidism of any type
 - Autoimmune disease (with the exception of inactive Hashimoto's thyroiditis)
 - Multiple sclerosis

- Unstable cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, metabolic, neurological, pulmonary, and/or renal disease
 - Current or recent neoplastic disease (ie, evaluable disease within the past 5 years), excluding localized basal cell carcinoma
 - Systemic infection
 - Any disease, disorder or condition that would have placed the subject at risk during the trial, interfered with the subject's or investigator's ability to measure change on any outcome measures and/or compromised the objectives outlined in the protocol
2. Subject had a history of myocardial infarction, transient ischemic attack, or cerebrovascular accident
 3. Subject had a Major Depressive Disorder (as defined by the Mini International Neuropsychiatric Interview [MINI]) or was currently being treated for a Major Depressive Disorder or had a history of psychotic disorder and/or bipolar disorder. Subjects being considered for discontinuation of antidepressant medication required careful evaluation as to any risks from cessation of antidepressant therapy. If, in the opinion of the investigator, a reasonable risk of resultant subject harm existed, the subject was to be excluded from study participation
 4. Subject had Generalized Anxiety Disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders IV, Text Revision
 5. Subject had any other problems that, in the investigator's opinion, would have precluded the subject's participation and completion of this trial or compromised reliable representation of subjective symptoms
 6. Subject had a MINI suicidality module score > 0 and/or answered "yes" to the suicide question (A3-g) on the Major Depressive Episode module of the MINI and/or greater than or equal to 1 on Question 9 of the Beck Depression Inventory-II (BDI-II)
 7. Subject had a current or past history of a substance use disorder including alcohol abuse as defined by the DSM-IV-TR.
 8. Subject had a clinically significant history of seizure disorder either past or present, a history of clinically significant head trauma (i.e., concussion resulting in clinically significant loss of consciousness), chronic persistent migraine headaches, or past invasive intracranial surgery
 9. Subject had known succinic semialdehyde dehydrogenase deficiency
 10. Subject had participated in a previous Xyrem (sodium oxybate) clinical trial (with the exception of subjects who, due to completion of enrollment for Xyrem Study 06-008, were withdrawn from the screening phase of Study 06-008 prior to being randomized)
 11. Subject had received acupuncture therapy intended for the treatment of fibromyalgia within 30 days prior to baseline
 12. Subject had taken GHB, sodium oxybate, or Xyrem at any time
 13. Subject had taken any investigational therapy within 2 months prior to signing the informed consent

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14. Subject was unable to discontinue prohibited medications during the washout period and throughout the duration of the trial. Subjects able to discontinue these medications may have participated in the study if they agreed to follow the investigator's recommended down-titration and washout program prior to study entry. If a subject must have discontinued any of these therapies, the investigator must have made an evaluation as to any risks from cessation of such therapies. If, in the opinion of the investigator, a reasonable risk of resultant subject harm existed, the subject must have been excluded from trial participation. Prohibited medications included the following categories:
- Anticonvulsants prescribed for any reason
 - All antidepressants (including but not limited to, tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs], or SNRIs, bupropion, trazodone), monoamine oxidase inhibitors, and monoamine oxidase-B inhibitors, such as selegiline)
 - Mood stabilizers such as lithium
 - Antipsychotic medications
 - Sleep aids such as hypnotics, tranquilizers, sedating antihistamines (nonsedating antihistamines were permitted during the trial), and benzodiazepines
 - Stimulant medications for any reason, including attention-deficit hyperactivity disorder, such as dextroamphetamine, methylphenidate, and modafinil
 - Nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and corticosteroids (short-term use of nasal, inhaled, and topical corticosteroids unrelated to the treatment of fibromyalgia was allowed)
 - Dopamine agonists and any other Parkinson's disease medications
 - Opioids
 - All medications taken for pain, including pain associated with osteoarthritis, or sleep disorders (except for allowed acetaminophen [paracetamol])
 - Skeletal muscle relaxants
 - Chemotherapy for neoplastic disease
 - Any other medications taken by the subject for the treatment of fibromyalgia except for acetaminophen (paracetamol) up to 4 g per day
15. Subject was experiencing clinically significant medication withdrawal symptoms after the withdrawal/washout period
16. Subject was experiencing fatigue and/or drowsiness/sedation in association with intake of allowed medications
17. Subject had an allergic reaction to GHB or sodium oxybate or any of its constituents (e.g., malic acid)
18. Subject had any of the following exclusionary clinical laboratory results:
- Serum creatinine greater than 2.0 mg/dL
 - Thyroid stimulating hormone (TSH) >6 µU/mL or <0.3 µU/mL

- Abnormal liver function tests (aspartate transaminase [AST] or alanine transaminase [ALT] more than twice the upper limit of normal)
 - Elevated serum bilirubin more than 1.5 times the upper limit of normal
 - Pretrial electrocardiogram (ECG) results demonstrating clinically significant arrhythmias or conduction delays
 - Positive pregnancy test at any time during the trial
 - Positive urine drug screen for drugs of abuse and/or positive alcohol test at screening or at Visit 4
19. Subject was diagnosed with sleep apnea and was not currently on stable CPAP therapy for the last 30 days prior to baseline
20. Subject had a BMI of greater than or equal to 40 kg/m²
21. Subject was on a sodium-restricted diet
22. Subject had a visual impairment or motor disturbance which precluded the capacity to make accurate notation on the electronic diary VAS scales
23. Subject had any of the following exclusionary socioeconomic factors:
- Pending worker's compensation litigation or other related monetary settlements or other pending litigation related to physical complaints
 - Subjects on disability or pending disability evaluation for chronic pain and/or fibromyalgia
 - An occupation that required variable shift work or routine night shifts
24. Female subject who was nursing or lactating
25. Subject had a history of porphyria

Appendix C: Efficacy Measures in the Fibromyalgia Clinical Program

Pain Visual Analog Scale (Pain VAS)

Pain severity was measured using a pain visual analog scale (VAS), which ranged from 0 (no pain) to 100 (worst imaginable pain). Electronic diaries were used to collect data on each subject's pain in the morning, afternoon, and evening of every day. The pain VAS was 5 centimeters long on the electronic diary. Measurements collected were converted to equivalent measurements on a 10-centimeter VAS for analysis, in accordance with the validated method of Jamison and colleagues (2002). The subject was instructed to "Please indicate your current pain level." The pain VAS line was featureless other than the phrases (no pain and worst imaginable pain) that anchored it at each end. Pain VAS data were collected three times daily from the beginning of the baseline period through the end of treatment (Week 14 in the Phase 3 controlled studies). (In Study 06-010, pain VAS was measured once daily in the evening, and the subject was instructed to "Please indicate your pain on the average for today.")

Fibromyalgia Impact Questionnaire (FIQ)

The FIQ is a 20-item questionnaire that was used to evaluate subject's current fibromyalgia functional status (Burckhardt et al. 1991). The Fibromyalgia Impact Questionnaire (FIQ) total score ranges from 0, indicating no impairment, to 100, indicating maximum impairment. It was designed to collect data on the total spectrum of problems associated with fibromyalgia and of responses to therapy and is considered a measure of functionality. FIQ subscales include "physical impairment," "did not feel good," "work missed," "difficulty with work," "pain," "fatigue," "tired upon awakening," "stiffness," "anxiety," and "depression." The FIQ was administered at each visit from the end of washout through the end of treatment (Week 14 in the Phase 3 controlled studies).

Fatigue Visual Analog Scale (Fatigue VAS)

The fatigue VAS scale ranged from 0 (no fatigue) to 100 (worst imaginable fatigue). The fatigue VAS has been previously used in clinical trials in fibromyalgia (Arnold et al. 2004b, Ribel-Madsen et al. 2007, Mease et al. 2008b), including one conducted by the authors of the original FIQ validation, despite not being validated as an outcome measure separate from the FIQ, of which it is a part (Burckhardt et al. 1991).

Electronic diaries were used to collect data on each subject's fatigue in the morning, afternoon, and evening of every day. The electronic diaries regularly transmitted their contents to a central database. The fatigue VAS was 5 centimeters long on the electronic diary. Measurements collected were converted to equivalent measurements on a 10-centimeter VAS for analysis. The subject was instructed to "Please indicate your current level of fatigue." The fatigue VAS line was featureless other than the phrases (no fatigue and worst imaginable fatigue) that anchored it at each end. Fatigue VAS data were collected three times daily from the beginning of the baseline period through the end of treatment (Week 14 in the Phase 3 controlled studies). (In Study 06-010, fatigue VAS was measured once daily in the evening, and the subject was instructed to "Please indicate your fatigue on the average for today.")

Patient Global Impression of Change (PGI-c)

The PGI-c asked subjects to rate their fibromyalgia since they started taking the study medication on a seven-point categorical scale (very much better, much better, a little better, no change, a little worse, much worse, and very much worse). The PGI-c was administered at Weeks 4 through 14 in the Phase 3 controlled studies.

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Short Form-36 (SF-36)

The SF-36 Quality of Life Questionnaire was used to collect information about how the study drug affected the subject's life ([Ware & Sherbourne 1992](#); [Ware et al. 1993, 2000](#)). The SF-36 Quality of Life Questionnaire ranges from 0 to 100, with higher scores indicating better functioning (each score is normalized to the 1998 population, with a mean of 50 and a standard deviation of 10). The SF-36 Physical Component Summary (PCS) is the component summary score related to physical functioning, a key domain used for rating multidimensional function in fibromyalgia studies.

Data from the Physical Component Summary (PCS), the Mental Component Summary (MCS), and the following eight domains were used for analysis: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The SF-36 presents certain questions as ordinal sets (e.g., all of the time, most of the time, etc.) rather than as dichotomous choices (e.g., yes or no). The SF-36 was administered with a 4-week recall period in the Phase 3 studies. The SF-36 was administered at the end of baseline and the end of treatment (Week 14 in the Phase 3 controlled studies).

Jenkins Sleep Scale (JS)

The JS is a short, four-question sleep disturbance survey, administered to collect information about how study drug affected the subject's sleep ([Jenkins et al. 1988](#)). The final score was the sum of individual question scores. For the following four items, the questions were all posed as "How often in the past month did you . . ."

1. Have trouble falling asleep?
2. Wake up several times per night?
3. Have trouble staying asleep (including waking up too early)?
4. Wake up after your usual amount of sleep feeling tired and worn out?

Each question was scored as: 0=not at all, 1=1 to 3 nights, 2=4 to 7 nights, 3=8 to 14 nights, 4=15 to 21 nights, and 5=22 to 31 nights for a total score range of 0-20, where higher scores indicate worse sleep disturbance. The JS was administered at the end of baseline, and at Weeks 4, 8, and 14 in the Phase 3 controlled studies.

Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ is a 30 question survey that was used to evaluate the impact of sleepiness or tiredness on daytime functioning on activities of daily life ([Weaver et al. 1997](#)). Subjects were asked to rate how much being "sleepy" or "tired" affected specific activities. Subjects were instructed that the words "sleepy" or "tired" describe feelings "that you can't keep your eyes open, your head is droopy, that you want to nod off or that you feel the urge to nap. These words do not refer to the tired or fatigued feeling you may have after you exercise." FOSQ questions were answered with following possible responses: N/A=I don't do this activity for other reasons; 1=yes, extreme; 2=yes, moderate; 3=yes, a little; and 4=no. The FOSQ was administered at the end of baseline, and at Weeks 8, 12, and 14 in the Phase 3 controlled studies.

The FOSQ total scores range from 5 to 20, with lower scores indicating greater difficulty in everyday functioning due to feeling "sleepy" or "tired." The FOSQ ([Weaver et al. 1997](#)) has been used to evaluate functionality in multiple medical conditions that feature disturbed sleep,

but has not been validated in the fibromyalgia population. In the Phase 3 trials, the FOSQ was used to determine the impact of sleepiness or tiredness on daytime functioning.

Manual Tender Point Survey (MTPS) Site Scores

The MTPS was used to measure how subjects rated their pain intensity at each tender point. In assessing tenderness using the MTPS, the investigator applied 4 kg of pressure to each of the 18 tender points. Each of the 18 possible tender points was rated by the subject on a 10-point scale in which 0 indicated no pain and 10 indicated the worst pain the subject ever experienced. The total score range was 0-180. Reductions in MTPS indicate a reduction in tenderness, an important symptom identified by patients with fibromyalgia ([Mease et al. 2009b](#)).

Tender point examinations were performed using the standardized protocol described in the MTPS by all investigators and examiners on all subjects at all required assessments. The survey included a description of pressure application techniques, procedural guidelines and patient instructions, survey site identification instructions, and the MTPS scoring sheet. MTPS site scores were collected at screening, the end of baseline, and the end of treatment (Week 14 in the Phase 3 controlled studies).

Fibromyalgia Syndrome Composite Response

This composite endpoint was defined as the proportion of subjects who met three criteria: achieved a PGI-c response of “very much better” or “much better,” had a $\geq 30\%$ reduction in pain VAS, and had a $\geq 30\%$ reduction in FIQ total score at Week 14 in the Phase 3 controlled studies. (In the Phase 2 study, the Fibromyalgia Syndrome Composite Response was the proportion of subjects who achieved a PGI-c response of “very much better” or “much better,” had a $\geq 20\%$ reduction in pain VAS, and had a $\geq 20\%$ reduction in FIQ total score.)

Epworth Sleepiness Scale (ESS)

This scale was used to collect subjective ratings of daytime sleepiness. The ESS is composed of 8 questions regarding likeliness of dozing off or falling asleep during activities such as sitting and reading, and watching TV. The final score is the sum of the individual scores of all 8 questions. Scores range from 0 to 24, with higher scores indicating a greater chance of dozing/falling asleep. The ESS was used only in the Phase 2 study.

Appendix D: Adverse Effects with Sodium Oxybate and the Three Approved Products for Fibromyalgia

Three drugs are currently approved in the US for the treatment of fibromyalgia: Lyrica[®] (pregabalin) Capsules CV (Pfizer Pharmaceuticals, LLC), Cymbalta[®] (duloxetine hydrochloride) Delayed-Release Capsules for Oral Use (Eli Lilly & Company), and Savella[®] (milnacipran hydrochloride) Tablets (Forest Pharmaceutical, Inc.). Duloxetine and milnacipran are selective serotonin and norepinephrine reuptake inhibitors (SNRIs) and pregabalin is an antiepileptic drug.

Adverse events reported in $\geq 5\%$ of fibromyalgia patients in clinical trials with these drugs (all dose levels combined) included the following:

- Pregabalin (n=1517): dizziness (38%), somnolence (20%), headache (12%), increased weight (11%), vision blurred (8%), dry mouth (8%), constipation (7%), fatigue (7%), euphoric mood (6%), peripheral edema (6%), sinusitis (5%), increased appetite (5%), disturbance in attention (5%), and balance disorder (5%) ([Lyrica US Prescribing Information 2009](#))
- Duloxetine (n=876): nausea (29%), headache (20%), dry mouth (18%), insomnia (16%), constipation (15%), fatigue (15%), diarrhea (12%), decreased appetite (11%), dizziness (11%), somnolence (11%), upper respiratory tract infection (7%), hyperhidrosis (7%), agitation (6%), dyspepsia (5%), musculoskeletal pain (5%) ([Cymbalta US Prescribing Information 2009](#))
- Milnacipran (n=1557): nausea (37%), headache (18%), constipation (16%), insomnia (12%), hot flush (12%), dizziness (10%), hyperhidrosis (9%), palpitation (7%), vomiting (7%), upper respiratory tract infection (6%), increased heart rate (6%), dry mouth (5%), migraine (5%), and hypertension (5%) ([Savella US Prescribing Information 2009](#)).

For sodium oxybate, the list of adverse events reported in $\geq 5\%$ of subjects who received any dose in the Phase 3 placebo-controlled trials (n=747) includes headache (20.6%), nausea (19.1%), dizziness (13.8%), diarrhea (8.0%), vomiting (7.1%), anxiety (6.3%), and nasopharyngitis (5.6%).

Appendix E: Postmarketing Listing of Deaths from Xyrem Commercial Experience^a			
Category	Age (years)	Gender (M/F)	Preferred Term
Overdose	UNK	Female	Multiple drug overdose ^b ;Unevaluable event
Overdose	35	Female	Multiple drug overdose ^b
Overdose	26	Female	Multiple drug overdose ^b ;Sedation;Intentional drug misuse;Initial insomnia
Overdose	51	Female	Overdose
Suicide	34	Female	Drug toxicity; drowning; completed suicide
Suicide	UNK	Female	Completed suicide;Abnormal behaviour;Feeling abnormal
Suicide	35	Male	Completed suicide;Depression;Stress
Suicide	55	Female	Completed suicide
Suicide	27	Male	Completed suicide
Suicide	30	Male	Completed suicide;Somnambulism;Tardive dyskinesia;Somnambulism;Somnolence;Incoherent
Other Medical Cause	57	Male	Acute myocardial infarction;Cardiac failure congestive;Death
Other Medical Cause	66	Female	Breast cancer
Other Medical Cause	UNK	Female	Breast cancer metastatic
Other Medical Cause	33	Male	Bronchopneumonia
Other Medical Cause	UNK	Female	Cardiac arrest; brain damage; coma
Other Medical Cause	61	Female	Chronic obstructive pulmonary disease
Other Medical Cause	49	Male	Cardiac death
Other Medical Cause	79	Male	Cardiac death
Other Medical Cause	45	Female	Cardiac disorder;Loss of consciousness
Other Medical Cause	68	Female	Choking;Cardio-respiratory arrest
^a Note: Cases are presented by category and AE primary preferred term. Secondary preferred terms are included when available. US data only. Based on 31,645 years of patient use. Information on relationship to drug is not included in this table. ^b Patient was taking multiple drugs, which may or may not have included Xyrem UNK - unknown			

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Appendix E: Postmarketing Listing of Deaths from Xyrem Commercial Experience^a			
Category	Age (years)	Gender (M/F)	Preferred Term
Other Medical Cause	72	Female	Coronary artery disease;Cardiac failure congestive;Diabetic complication;Chronic obstructive pulmonary disease;Cataplexy
Other Medical Cause	46	Female	Coronary artery disease
Other Medical Cause	44	Female	Drowning
Other Medical Cause	66	Female	Lung neoplasm malignant
Other Medical Cause	75	Male	Hepatic neoplasm malignant;Ammonia increased;Loss of consciousness;Eye movement disorder;Aphasia
Other Medical Cause	79	Female	Leukaemia
Other Medical Cause	56	Male	Lung neoplasm malignant; respiratory failure; pleural effusion; respiratory distress; metastases to bone; dyspnoea; metastatic pain; sedation; weight decreased
Other Medical Cause	61	Female	Lung neoplasm malignant
Other Medical Cause	75	Male	Lung neoplasm malignant
Other Medical Cause	81	Female	Lymphoma;Cardiac operation
Other Medical Cause	46	Female	Malaise
Other Medical Cause	UNK	Male	Malaise;Neoplasm malignant
Other Medical Cause	UNK	Male	Myocardial infarction
Other Medical Cause	46	Female	Myocardial infarction;Respiratory failure;Sleep apnoea syndrome;Arrhythmia
Other Medical Cause	52	Female	Palpitations;Dysgeusia;Death
Other Medical Cause	80	Male	Parkinson's disease
Other Medical Cause	UNK	Female	Renal failure
Other Medical Cause	43	Female	Road traffic accident;Hepatic haemorrhage;Hepatic failure;Renal failure;Brain death;Headache;Traumatic liver injury
Other Medical Cause	79	Male	Upper gastrointestinal haemorrhage;Fall
<p>*Note: Cases are presented by category and AE primary preferred term. Secondary preferred terms are included when available. US data only. Based on 31,645 years of patient use. Information on relationship to drug is not included in this table.</p> <p>UNK - unknown</p>			

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Appendix E: Postmarketing Listing of Deaths from Xyrem Commercial Experience*					
Category	Age (years)	Gender (M/F)	Preferred Term	Multiple Medications (Y/N)	No. Attempts to Obtain Additional Information
Cause Unidentified	21	Male	Death	N	4
Cause Unidentified	26	Male	Death	N	3
Cause Unidentified	31	Female	Death	N	1
Cause Unidentified	32	Female	Death;Post procedural complication	N	3
Cause Unidentified	36	Male	Death	Y	1
Cause Unidentified	37	Male	Death	N	2
Cause Unidentified	38	Female	Death	Y	2
Cause Unidentified	38	Female	Death	Y	1
Cause Unidentified	41	Female	Death	N	2
Cause Unidentified	44	Male	Death;Drug ineffective;Cognitive disorder;Sleep paralysis	Y	1
Cause Unidentified	45	Female	Death	Y	2
Cause Unidentified	45	Female	Death	N	4
Cause Unidentified	45	Female	Death	N	1
Cause Unidentified	47	Male	Death	N	2
Cause Unidentified	48	Female	Death	N	2
Cause Unidentified	48	Male	Death	Y	3
Cause Unidentified	48	Female	Death	N	1
Cause Unidentified	48	Male	Death;Somnambulism;Enuresis	N	4
Cause Unidentified	48	Female	Death	N	3
Cause Unidentified	49	Female	Death;Memory impairment	Y	1
Cause Unidentified	50	Female	Death	N	2
Cause Unidentified	50	Male	Death	N	2
Cause Unidentified	51	Male	Death	N	3
Cause Unidentified	53	Female	Death	Y	2
Cause Unidentified	53	Female	Death	N	7
<p>*Note: Cases are presented by category and AE primary preferred term. Secondary preferred terms are included when available. US data only. Based on 31,645 years of patient use. Information on relationship to drug is not included in this table.</p> <p>UNK - unknown</p>					

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Appendix E: Postmarketing Listing of Deaths from Xyrem Commercial Experience*					
Category	Age (years)	Gender (M/F)	Preferred Term	Multiple Medications (Y/N)	No. Attempts to Obtain Additional Information
Cause Unidentified	54	Female	Death	N	4
Cause Unidentified	54	Male	Death	N	3
Cause Unidentified	55	Male	Death;Hospitalisation;Hypertension	N	3
Cause Unidentified	56	Female	Death	Y	4
Cause Unidentified	56	Female	Death	N	4
Cause Unidentified	58	Female	Death	Y	0
Cause Unidentified	59	Female	Death	N	3
Cause Unidentified	62	Male	Death	N	1
Cause Unidentified	65	Female	Death	N	3
Cause Unidentified	70	Female	Death	Y	2
Cause Unidentified	79	Male	Death	N	2
Cause Unidentified	81	Male	Death	N	2
Cause Unidentified	87	Male	Death	N	1
Cause Unidentified	88	Female	Death	N	4
Cause Unidentified	UNK	Male	Death	N	1
Cause Unidentified	UNK	Female	Death	N	3
Cause Unidentified	UNK	Female	Death;Dehydration;Viral infection; Drug dose omission	Y	2
Cause Unidentified	UNK	Male	Death	N	2
Cause Unidentified	UNK	Male	Death;Hallucination, auditory	N	2
<p>*Note: Cases are presented by category and AE primary preferred term. Secondary preferred terms are included when available. US data only. Based on 31,645 years of patient use. Information on relationship to drug is not included in this table. UNK - unknown</p>					

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